

An investigation of the role of antenatal
depression, maternal cortisol and postnatal
interactive behaviour on infant
neurodevelopment in the first year of life.

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I. Declaration

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II. Summary

Major Depressive Disorder (MDD) is the most prevalent psychiatric disorder during the perinatal period. If left undisclosed or untreated, MDD can have lasting adverse effects on maternal wellbeing and lead to adverse developmental consequences for her baby. This aim of this thesis was to investigate the relationship between antenatal depression and infant neurodevelopment across the first year of life. A number of pathways are proposed to underlie the relationship between antenatal depression and infant outcomes. Two of these were explored: (i) the association between antenatal cortisol and infant neurodevelopment and (ii) the association between maternal perinatal depression and maternal interactive behaviour.

Three groups of pregnant women were recruited to take part in this study: women with a current diagnosis of MDD (Depressed), women with one or more previous episodes of MDD (History) and healthy women with no previous diagnosis of psychiatric disorder (Control). Maternal mood and cortisol were measured during pregnancy and mothers and their infants were followed up at two, six and twelve months. Maternal mood, infant neurodevelopment and mother-infant interactive behaviour were measured at each postpartum time-point.

Assessment of infant neurodevelopment indicated no group differences at two or six months suggesting no association between maternal antenatal depression and infant neurodevelopment at these time-points. At twelve months, infants in the Depressed group had lower language scores compared to infants in the Control group. However this difference attenuated after controlling for maternal concurrent depression. Maternal antenatal cortisol was correlated with a number of infant measures at two months, infant cognitive development at six months and motor development at twelve months.

Mother-infant interactions recorded at each time-point were coded for affect, maternal linguistic input and maternal vocal responsiveness. At two months, mother-infant dyads in the History group demonstrated a higher proportion of shared positive affect in comparison to controls. No group differences were observed for maternal interactive behaviour at any of the remaining measures or time-points. One aspect of maternal interactive behaviour, mean length of utterance (MLU) was associated with postnatal depression and indirectly associated with antenatal depression.

Lastly, the relationships between maternal interactive behaviour and infant neurodevelopment were assessed. Maternal positive affect, maternal-infant matched affect, lexical and syntactical complexity were associated with different aspects of infant neurodevelopment, indicating the role of the *specificity* of maternal behaviour in infant developmental outcomes. In addition, maternal behaviour moderated the relationship between antenatal cortisol and infant cognitive and motor development suggesting that more optimum levels of maternal interactive behaviour are associated with better infant outcomes.

This study indicated that maternal antenatal depression is not reliably associated with adverse outcomes for her infant. These findings suggest evidence of a 'programming' effect of antenatal cortisol on the developing fetus with implications for infant neurodevelopment in the first postnatal year. This study provides evidence that these adverse effects can be precluded in the context of a supportive postnatal environment. Further investigation of the characteristics of the fetal and early life environment may provide better insight as to the potential factors which can impair or indeed support optimum mother and infant outcome across the perinatal period.

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IV Table of Contents

Chapter 1: Introduction	19
1.1 Overview	20
1.1.2 Antenatal Depression.....	21
1.1.3 Risk Factors associated with antenatal depression	22
1.1.4 Outcomes of Antenatal Depression on the infant	22
1.1.5 Antenatal depression and obstetric outcomes.....	23
1.1.6 Antenatal depression and Infant Temperament	23
1.1.7 Antenatal depression and neurodevelopment.....	24
1.1.8 Antenatal depression and the increased risk of emotional disorders in childhood and adulthood	25
1.2 Neurobiological Mechanisms of Antenatal Depression.....	25
1.2.1 The Hypothalamic Pituitary Adrenal Axis.....	27
1.2.2 The hypothalamic pituitary adrenal axis and pregnancy	29
1.2.3 HPA axis and Depression.....	29
1.2.4 Epigenetic alterations at the glucocorticoid receptor	32
1.2.5 Maternal behaviour in pregnancy	32
1.2.6 Glucocorticoids as a mediator of infant and child outcomes	33
1.3 Early life programming and the role of maternal care	35
1.3.1 Maternal care in the postnatal environment	35
1.3.2 Maternal-infant affective matching.....	37
1.3.3 Maternal speech behaviour	39
1.3.4 The impact of postnatal depression on maternal caregiving ability	41
1.3.5 Postnatal depression and maternal affective expression	43
1.3.6 Postnatal depression and maternal vocalisation behaviour	44
1.3.7 Antenatal depression and mother-infant interaction.....	45
1.3.8 The moderating role of maternal caregiving on infant physiological and developmental outcomes	46
1.4 Aims and Structure of the thesis.....	48
Chapter 2: Method.....	50
2.1. Study Design and overview.....	51
2.1.1 Contribution of work by the author.....	51
2.1.2 Ethical Considerations.....	52

2.2.1	Participants	53
2.2.2	Group Criteria.....	53
2.2.3	Inclusion and Exclusion Criteria	53
2.2.3	Participant Recruitment	53
2.2.4	Recruitment Procedure	55
2.3	Measures.....	57
2.3.1	Demographic Characteristics	57
2.3.2	Maternal health behaviours and obstetric factors	57
2.3.3	Maternal Clinical Measures.....	58
2.3.4	Infant Measures	60
2.3.4	Biological Measures	65
2.3.5	Maternal-Infant Interaction	67
2.4	Statistical Analyses	73
Chapter 3: Antenatal depression and infant neurodevelopment in the first postnatal year		75
3.1	Introduction	76
3.1.1	Clinical diagnosis and self-report symptoms of mood....	77
3.1.2	Antenatal depression and infant neurobehavioural development in the early postpartum period.....	77
3.1.3	Antenatal depression and infant neurodevelopment within the first year and beyond.....	78
3.1.4	Study outline	79
3.2	Method.....	81
3.2.1	Participants	81
3.2.2	Maternal Measures.....	81
3.2.3	Infant Measures	82
3.2.4	Statistical Analyses	84
3.3.	Results	86
3.3.1	Flow of participants.....	86
3.3.2	Demographic Characteristics	87
3.3.3	Health Characteristics	88
3.3.4	Maternal Measures of mood during pregnancy and postpartum.....	88
3.3.5	Infant demographic and birth characteristics.....	96
3.3.6	Neonatal Behavioural Assessment Scale	97
3.3.7	Bayley Scale of Infant Development	100
3.4	Discussion.....	111

3.4.1	Overview of Results	111
3.4.2	Trajectories of Depression across the perinatal period.	112
3.4.3	Infant Neurobehavioral Development at two months: Neonatal Behavioural Assessment Scale	112
3.4.4	Bayley scale of Infant development at 6 and 12 months	114
3.4.5	Social-Emotional and Adaptive Behaviour Scales	116
3.4.6	Conclusions	117
Chapter 4: Maternal hypothalamic pituitary adrenal axis activity during pregnancy and infant neurodevelopment		118
4.1.	Overview	119
4.1.1	The Hypothalamic-Pituitary-Adrenal axis	119
4.1.2	The maternal HPA axis in pregnancy	120
4.1.3	Antenatal depression and the HPA axis	121
4.1.4	Impact of exposure to higher levels of cortisol on infant development	121
4.1.5	Methodological issues within the literature	122
4.1.6	Study Outline	124
4.2.1	Method.....	126
4.2.2	Participants	126
4.2.3	Measures.....	126
4.2.3	Biological Measures	129
4.2.4	Statistical Analyses.....	130
4.3	Results.....	131
4.3.1	Maternal antenatal cortisol and NBAS clusters	131
4.3.2	Maternal antenatal cortisol and the NBAS supplementary items.	131
4.3.3	Maternal antenatal cortisol and the subscales of the BSID.	134
4.4	Discussion.....	137
4.4.1	Antenatal Cortisol and the Neurobehavioral Development.....	137
4.4.2	Antenatal Cortisol and the Bayley scale of Infant development	139
4.4.3	Antenatal Cortisol and the Social-Emotional and Adaptive Behaviour Scales	141
4.4.4	Antenatal Cortisol Measurement	142

4.4.5	Conclusions	144
Chapter 5: Associations between maternal antenatal and postnatal depression with maternal-infant interactive behaviour..... 145		
5.1.	Introduction	146
5.1.1	Maternal and infant matched affective expression	147
5.1.2	Maternal Linguistic Complexity and Vocal Responsiveness	148
5.1.3	Study Outline.....	149
5.2	Method.....	151
5.2.1.	Participants	151
5.2.2	Measures.....	151
5.2.3	Maternal-Infant Interaction	152
5.2.4	Statistical Analyses	156
5.3	Results	158
5.3.1	Group Comparisons.....	158
5.3.2	Maternal Depression and Interactive Behaviour	167
5.4.	Discussion.....	175
5.4.1	Maternal Linguistic Complexity.....	175
5.4.2	Maternal Vocal Responsiveness.....	177
5.4.3	Maternal and Infant Matched Affect	179
5.4.4	Methodological considerations for video recorded interactions	181
5.4.5	Conclusions	183
Chapter 6 Maternal-infant interactive behaviour and infant neurodevelopment 184		
6.1	Introduction	185
6.1.1	Shared Mother-Infant Affective State and Infant Outcomes	186
6.1.2	Maternal Linguistic Input and Infant Outcomes	187
6.1.3	Moderating effect of maternal interactive behaviour on infant developmental outcomes	190
6.1.4	Study Outline.....	191
6.2	Method.....	193
6.2.1.	Participants	193
6.2.2	Measures.....	193
6.2.3	Maternal Salivary Cortisol	196
6.2.4	Maternal-Infant Interaction	196

6.2.5	Statistical Analyses.....	201
6.3	Results.....	203
6.3.1	Maternal Interactive Behaviour and Infant Neurodevelopment at Two Months	203
6.4.2	Maternal Interactive Behaviour and Neurodevelopment at Six months.....	210
6.4.3	Maternal Interactive Behaviour and Neurodevelopment at Twelve Months	215
6.4.4	Associations between maternal antenatal cortisol and infant neurodevelopment.....	220
6.4.5	The combined influence of maternal antenatal evening cortisol and maternal interactive behaviour on infant cognitive development at six months.....	220
6.4.6	The combined influence of maternal cortisol awakening response and maternal interactive behaviour and infant motor development at twelve months.....	224
6.4	Discussion.....	227
6.5.1	Maternal affect, matched affect and infant NBAS scores at two months.....	228
6.5.2	Maternal linguistic complexity and responsiveness	230
6.5.3	Maternal Positive Affect	233
6.5.4	Moderation Effect of Maternal Postnatal Interactive Behaviour.....	233
6.5.5	Maternal Response latency and switching pause duration	235
6.5.6	Conclusions	236
Chapter 7: Discussion and Conclusions		238
7.1	Introduction	239
7.2	Antenatal depression and infant neurodevelopment	239
7.3	Antenatal cortisol and infant neurodevelopment	242
7.4	Maternal Depression and the association with postnatal interactive behaviour.....	246
7.5	Maternal interactive behaviour and infant neurodevelopment	247
7.6	Moderating effect of maternal interactive behaviour on infant outcome	251
7.7	Strengths and limitations of the current study.....	252
7.8	Future Directions	255
7.9	Conclusions	256

V List of Figures

Figure 1.1:	The maternal HPA axis during pregnancy.....	23
Figure 2.1	Flow chart indicating the pathways through which participants were recruited to the study.....	54
Figure 2.2	Administration Sequence for the Neonatal Behavioural Assessment Scale.....	61
Figure 2.3	Cortisol awakening response parameters.....	66
Figure 3.1	Flow chart of study participants.....	85
Figure 3.2	Hamilton Rating Scale for Depression scores across groups and time-points.....	90
Figure 3.3	Center for Epidemiological Studies Depression Scale scores across groups and time-points.....	91
Figure 3.4	Perceived Stress Scale scores across groups and time-points.....	92
Figure 3.5	Trajectories of mean Hamilton Rating Scale for Depression scores for each group.....	93
Figure 3.6	Trajectories of mean Center for Epidemiological Studies Depression Scale for each group.....	93
Figure 3.7	Trajectories of mean Perceived Stress Scale scores for each group.....	94
Figure 3.8	Group comparisons of mean scores for the Neonatal Behavioural Assessment scale clusters at two month.....	97
Figure 3.9	Group comparisons of mean scores for the Neonatal Behavioural Assessment scale supplementary items at two months.....	99
Figure 3.10	Group comparisons of mean scores for the Bayley Scales of Infant Development subscales at six months.....	101
Figure 3.11	Group comparisons of mean scores for the Bayley Scales of Infant Development subscales at six months.....	102
Figure 3.12	Group comparisons of mean scores for the Social-Emotional Scales at two, six and twelve months.....	107
Figure 3.13	Group comparisons of mean scores for the Adaptive Behaviour Scales at two, six and twelve months.....	107

Figure 5.1	Model of the association between antenatal depression and maternal mean length of utterance at two months mediated by two month HAM-D score.....	172
Figure 5.2	Model of the association between antenatal depression and maternal mean length of utterance at twelve months mediated by twelve month CES-D score.....	173
Figure 6.1	Simple Slopes equations of the regression of antenatal evening cortisol on six month cognitive development at three levels of total matched affect.....	222
Figure 6.2	Simple Slopes equations of the regression of antenatal cortisol awakening response on twelve month motor development at three levels of lexical complexity	225

VI List of Tables

Table 2.1	Overview of maternal and infant measures at each time-point.....	56
Table 2.2	Categories of depression severity with corresponding HAM-D scores.....	58
Table 2.3	NBAS seven cluster scoring criteria.....	62
Table 2.4	Video-recordings available for the mother-infant dyads in each group.....	70
Table 2.5	Inter-rater reliability values for Kappa and percentage agreement.....	71
Table 2.6	Sample size requirements for group and continuous analyses calculated post-hoc.....	73
Table 3.1	Demographic characteristics of the sample.....	86
Table 3.2	Health characteristics of the sample.....	87
Table 3.3	Mean scores for the measures of maternal mood during pregnancy.....	89
Table 3.4	Infant demographic and birth characteristics.....	96
Table 3.5	Mean scores and group comparisons for NBAS clusters.....	97
Table 3.6	Mean scores and group comparisons for NBAS supplementary items.....	98
Table 3.7	Mean scores for BSID subscales at six and twelve months.....	100
Table 3.8	Regression coefficients for group comparisons on the BSID subscales at six months.....	103
Table 3.9	Regression coefficients for group comparisons on the BSID subscales at twelve months.....	104
Table 3.10	Mean scores for SE and AB scales at two, six and twelve months.....	105
Table 3.11	Regression coefficients for group comparisons on the SE and AB subscales at two month.....	108
Table 3.12	Regression coefficients for group comparisons on the SE and AB subscales at six months.....	109

Table 3.13	Regression coefficients for group comparisons on the SE and AB subscales at twelve months.....	110
Table 4.1	Associations between antenatal cortisol indices and NBAS clusters prior to adjusting for multiple comparisons.....	132
Table 4.2	Associations between antenatal cortisol indices and NBAS supplementary items.....	133
Table 4.3	Associations between antenatal cortisol indices and subscales of the BSID at six and twelve months.....	135
Table 4.4	Associations between antenatal cortisol indices and the SE and AB subscales of the BSID at two, six and twelve months.....	136
Table 5.1	Descriptive data and group comparisons for MLU and <i>vocd</i> at each time-point.....	159
Table 5.2	Descriptive data and group comparisons for maternal mean response latency and switching pause duration at each time-point.....	160
Table 5.3	Descriptive data and group comparisons for percentage of maternal negative, neutral and positive affect at each time-point.....	162
Table 5.4	Descriptive data and group comparisons for percentage of infant negative, neutral and positive affect at each time-point.....	164
Table 5.5	Descriptive data and group comparisons for percentage of mother-infant matched positive, neutral and overall affect at each time-point.....	166
Table 5.6	Regression coefficients for the associations between maternal HAMD scores and maternal MLU at each time-point.....	168
Table 5.7	Regression coefficients for the associations between maternal CESD scores and maternal MLU at each time-point.....	169
Table 5.8	Regression coefficients for the associations between maternal HAMD scores and maternal <i>vocd</i> at each time-point.....	170
Table 5.9	Regression coefficients for the associations between maternal CESD scores and maternal <i>vocd</i> at each time-point.....	171

Table 6.1	Associations between maternal positive affect and maternal-infant matched affect and the NBAS clusters at two months.....	207
Table 6.2	Associations between maternal positive affect and maternal-infant matched affect and the NBAS supplementary items at two months.....	208
Table 6.3	Regression coefficients for the associations between maternal interactive behaviour and the SE and AB subscales of the BSID at two months.....	209
Table 6.4	Regression coefficients for the associations between maternal interactive behaviour and the BSID subscales at six months.....	213
Table 6.5	Regression coefficients for the associations between maternal interactive behaviour and the SE and AB subscales of the BSID at six months.....	214
Table 6.6	Regression coefficients for the associations between maternal interactive behaviour and the BSID subscales at twelve months.....	218
Table 6.7	Regression coefficients for the associations between maternal interactive behaviour and the SE and AB subscales of the BSID at twelve months.....	219
Table 6.8	B coefficients pertaining to the interaction terms considered in each regression model and infant cognitive development at six months.....	224
Table 6.9	B coefficients pertaining to the interaction terms considered in each regression model and infant motor development at twelve months.....	226

VI List of Abbreviations

11-β-HSD-2:	11 beta hydroxysteroid dehydrogenase
AB:	Adaptive Behaviour scale
ABN:	Arch-Back Nursing
AUC:	Area under the Curve
AUCg:	Area under the curve with respect to ground
AUCi:	Area under the curve with respect to increase
BSID:	Bayley Scales of Infant Development
CAR:	Cortisol Awakening response
CES-D:	Centre for Epidemiological Studies-Depression Scale
CWIUH:	Coombe Women and Infants' University Hospital
HAM-D:	Hamilton Rating Scale for Depression
HPA Axis:	Hypothalamic-Pituitary-Adrenal Axis
LG:	Licking and Grooming
MLU:	Mean Length of Utterance
NBAS:	Neonatal Behavioural Assessment Scale
NMH:	National Maternity Hospital
PND:	Post-natal Depression
PSS:	Perceived Stress Scale
RL:	Response Latency
SE:	Social Emotional scale
SP	Switching Pause
Vocd:	Lexical complexity

Chapter 1

Introduction

1.1 Overview

Motherhood is often alluded to as the 'happiest time of a woman's life', an ideal which places immense pressure on pregnant women and new mothers to feel as such. Although it is true that this time can be filled with ceaseless reward, joy and pride, it is also a time of great emotional challenge for most women and is accompanied by tremendous exhaustion, physical effort and personal sacrifice. Across the course of their lifetime, women have a twofold higher risk of developing depression compared with men (WHO, 2009). The peak of incidence for affective disorders occurs between the ages of 25-44 years which coincides with the reproductive years for the majority of women (Regier et al., 1988; Epperson, 1999). Depression is the most prevalent psychiatric disorder during the perinatal period (WHO, 2009) and if left undisclosed or untreated, can have lasting adverse effects on maternal wellbeing as well as developmental consequences for her baby throughout infancy, into childhood and potentially adulthood.

1.1.2 Antenatal Depression

Depression currently affects approximately 300 million people worldwide causing significant impairment in work, school, family functioning and, at worst, can lead to suicide (WHO, 2018). According to DSM-V (DSM-V, 2013) Major Depressive Disorder (MDD) is characterised by depressed mood or loss of interest or pleasure in everyday activities which is persistent for at least two consecutive weeks. In addition, at least five of the following symptoms must also be present: an increase or decrease in appetite, weight or sleep; presence of fatigue; feelings of worthlessness or guilt; difficulties with concentration; psychomotor agitation or retardation and recurrent thoughts of death or dying with or without suicidal thoughts or behaviour. These symptoms must occur for a period of at least two consecutive weeks; must cause distress or impairment within daily functioning and must not be due to intake of a substance or another medical condition. According to DSM-V, MDD with 'peripartum onset' is diagnosed when the onset of the symptoms outlined above occur during pregnancy or in the four weeks following delivery. However within applied settings, the time period within which perinatal depression is diagnosed extends from pregnancy to twelve months post-delivery (Milgrom & Gemmill, 2014).

Pregnancy, in particular, presents a time of increased vulnerability for the onset of depression in women, with many women experiencing their first onset of depression during this time. Overall prevalence rates for the occurrence of antenatal depression vary widely between studies, countries and populations. In high-income countries the prevalence rate is estimated to fall anywhere between 7-20%, whereas in developing countries this rate has been estimated at 20% or more (Biaggi et al., 2015). In Ireland, the *Well Before Birth* study reported that rates of antenatal depression symptoms occurred in approximately 16% of women (Jairaj et al., 2018)

1.1.3 Risk Factors associated with antenatal depression

Pregnancy is a time of increased risk for depression due to several factors. Firstly, hormonal fluctuations, such as the increasing levels of estrogen and progesterone that occur during gestation, have been proposed to provide a 'window of vulnerability' for the occurrence of depression and other mood symptoms (Soares & Zitek, 2008). Secondly, pregnancy and impending motherhood present a major life change and shift in circumstance which constitutes a further risk factor for the onset of depression (NIMH, 2018). Additional risk factors may further increase a woman's susceptibility to antenatal depression. These risks include: a previous history of psychiatric illness, exposure to adversity in early life such as childhood abuse, unplanned pregnancy, fears around childbirth, lack of partner or social support, younger age, lower educational attainment, unemployment, financial difficulties, current or past pregnancy complications, smoking, alcohol consumption and substance abuse (Biaggi et al., 2015; Lancaster et al., 2010).

1.1.4 Antenatal depression and infant outcomes

Antenatal depression is increasingly becoming recognised as a risk factor for a number of adverse outcomes during birth, the postnatal period and into later childhood and adulthood. The impact of antenatal depression on birth and infant outcomes including temperament and affective behaviour, neurodevelopment, psychopathology and susceptibility to later emotional difficulties will be outlined in the sections below.

1.1.5 Antenatal depression and obstetric outcomes

Antenatal depression is associated with a number of obstetric complications which can adversely impact the mother and the developing fetus both during pregnancy and at birth. Mothers with depression during pregnancy have an increased risk for pre-eclampsia (Kurki et al., 2000) and bleeding during gestation (Preti et al., 2000). Antenatal depression is also associated with spontaneous pre-term birth (<37 weeks) (Sion et al., 2015; Orr & Miller 1995), increased use of epidural analgesia (Chung et al., 2001), increased risk for delivery by emergency caesarean section (Hu et al., 2015; Bayrampour et al., 2001) and lower birth-weight (Accortt et al., 2015). Larger relative risks have also been reported for obstetric complications when depression is clinically diagnosed and remains untreated (Grote et al., 2010; Wisner et al., 2009).

1.1.6 Antenatal depression and infant temperament

Numerous studies have presented evidence of an association between antenatal depression and an increased likelihood of observed negative affectivity in infants. Infants born to mothers with antenatal depressive symptoms are reported to have a more difficult or fearful temperament, display more negative behavioural reactivity in the form of increased motor and cry activity in response to novel stimuli and are more likely to display excessive levels of crying (Davis et al., 2004; Werner et al., 2007; van der Wal, 2007; McGrath et al., 2008; Alvik et al., 2011; Della Vedova et al., 2014; Davis et al., 2007; Mebert, 1991; Rouse & Goodman, 2014). However the evidence associating maternal antenatal depression with the increased likelihood of a display of infant negative affect remains equivocal with many studies in this area reporting no association between antenatal depression and infant temperament (e.g. Rothenberger et al., 2011; Austin et al., 2005). Contradictory findings are due in part to

methodological differences between studies reported (e.g. maternal report vs directly observed behaviour). Due to this methodological variability, additional research in this area will need to be completed in order to draw conclusions as to the impact of antenatal depression on infant behavioural reactivity (Erickson et al., 2017).

1.1.7 Antenatal depression and neurodevelopment

One aspect of the literature on antenatal depression which is frequently overlooked is that of infant and child neurodevelopment, more specifically, the impact of depression during pregnancy on offspring cognitive, language and motor development. Behavioural and social-emotional issues frequently co-occur with neurodevelopmental delay and some aspects of neurodevelopment such as cognition can be predictive of psychopathology later in life (Gale et al., 2008; Bornstein et al., 2010). Currently, those studies which have investigated the impact of antenatal depression on infant neurodevelopment have reported inconsistent findings. Where some have reported a negative impact of antenatal depression on infant neurodevelopment (Koutra et al., 2013; Schechter et al., 2017), others have reported no association (Tse et al., 2010; Hay et al., 2008), or even a positive association (DiPietro et al., 2006). The research that has been published in this area has primarily measured neurodevelopment in children of school-age and older, leaving us with little knowledge of the impact of antenatal depression on developmental trajectories of cognition, language and motor skills in early childhood. Additionally, while efforts have been made to control for maternal depression in the period since birth, or maternal depression occurring at the time of child assessment, there are often large gaps where maternal mood is not accounted for. This is of particular importance due to the evidence

indicating that infants exposed to longer or repeated episodes of maternal depression during their early life have more behavioural issues and lower vocabulary scores (Brennan et al., 2000). Due to the high likelihood of a recurrence of depression for the mother during her child's early life, this is a crucial factor to consider and control for in research of this nature.

1.1.8 Antenatal depression and the increased risk of emotional disorders in childhood and adulthood

Beyond infancy, numerous studies have reported significant associations between antenatal depression and the increased risk of developing emotional and behavioural difficulties in childhood and later adulthood. Data from two longitudinal studies, the Avon Longitudinal Study of Parents and Children (ALSPAC) and a Finnish cohort study reported that elevated symptoms of depression during pregnancy are associated with an increased risk of child hyperactivity, emotional symptoms, conduct problems and problems with peer relationships during childhood (Leis et al., 2014; Lahti et al., 2016). Additional studies have also linked antenatal depressive symptoms with a higher risk of attentional problems, ADHD symptomology and an increased risk of depression in late adolescence (Van Batenburg-Eddes et al., 2013; Wolford et al., 2017; Pawlby et al., 2009; Pearson et al., 2013). Although exposure to maternal depressive symptoms in both the antenatal and postpartum period is associated with a higher risk of adverse outcomes for infants and older children (Brennan et al., 2000), the associations outlined above remain after controlling for maternal postnatal depressive symptoms.

1.2 Neurobiological Mechanisms of Antenatal Depression

The Developmental Origins of Health and Disease (DOHaD) hypothesis proposes that early life experiences, particularly within the intrauterine environment, play

a role in an individual's risk for chronic illness later in life (O'Donnell & Meaney, 2017). David Barker and his colleagues were the first proponents of this concept and proposed the 'fetal programming' hypothesis to explain the link between inadequate early nutrition and the increased susceptibility for developing Type 2 diabetes later in life (Hales & Barker, 1992). The concept of fetal programming has since been applied to explain the fetal origins of mental health, highlighting fetal vulnerability to early developmental influences and the importance of maternal well-being during pregnancy (O'Donnell & Meaney, 2017).

The Fetal programming hypothesis suggests that the developing fetus physiologically adapts to conditions within the intrauterine environment. Environmental events, such as inadequate maternal nutrition or increased levels of maternal stress, can alter the conditions of the intrauterine environment which modifies the structure and function of the developing brain. The extent of these effects vary according to sensitive periods in brain development and can impact subsequent child development and have lasting consequences which can continue through to adulthood (Glover, O'Connor and O'Donnell, 2010). The DOHaD hypothesis has been proposed as the 'third' pathway through which an increased susceptibility to psychopathology later in life can be transmitted to offspring, alongside that of genetic heritability and the influence of the postnatal environment (Monk et al., 2016). However, the mechanisms through which these three pathways exert their influence, or indeed how they interact with each other, are still not fully understood. One of the most likely mechanisms to explain the fetal origins of mental health originates with the body's stress response system, the Hypothalamic-Pituitary-Adrenal (HPA) axis and its end product, cortisol. This is of particular importance during pregnancy due to the changes that occur in the maternal HPA axis across gestation.

1.2.1 The Hypothalamic Pituitary Adrenal Axis

The Hypothalamic-Pituitary-Adrenal (HPA; Figure 1) axis comprises the body's stress response system which is responsible for the release of the glucocorticoid, cortisol (Giesbrecht, Campbell, Letourneau, Kooistra, Kaplan et al., 2012). Cortisol plays an important role in facilitating adaptation to stressful situations and restoration of homeostasis in humans (Miller and O'Callaghan, 2002). When faced with a stressor, a cascade of events commences when corticotropin releasing hormone (CRH) and arginine vasopressin (AVP) are released from the paraventricular nucleus of the hypothalamus. This signals the release of ACTH from the anterior pituitary gland which then stimulates the release of cortisol from the adrenal cortex. The HPA axis operates as a negative feedback loop where, following secretion, cortisol binds to receptors in the pituitary gland and hypothalamus. Cortisol binding at these receptors signals a halt to the further release of cortisol. This prevents chronic exposure to cortisol within the brain. Excessive exposure of brain tissue to cortisol can have damaging effects on structure and function (Waffarn & Davis, 2012). In addition to operating as a stress response system, basal HPA axis activity has a distinct diurnal rhythm characterised by a peak in cortisol approximately 20-30 minutes after waking, known as the Cortisol Awakening Response (CAR) and a subsequent decline of cortisol levels throughout the day (Edwards, Clow, Evans & Hucklebridge, 2001).

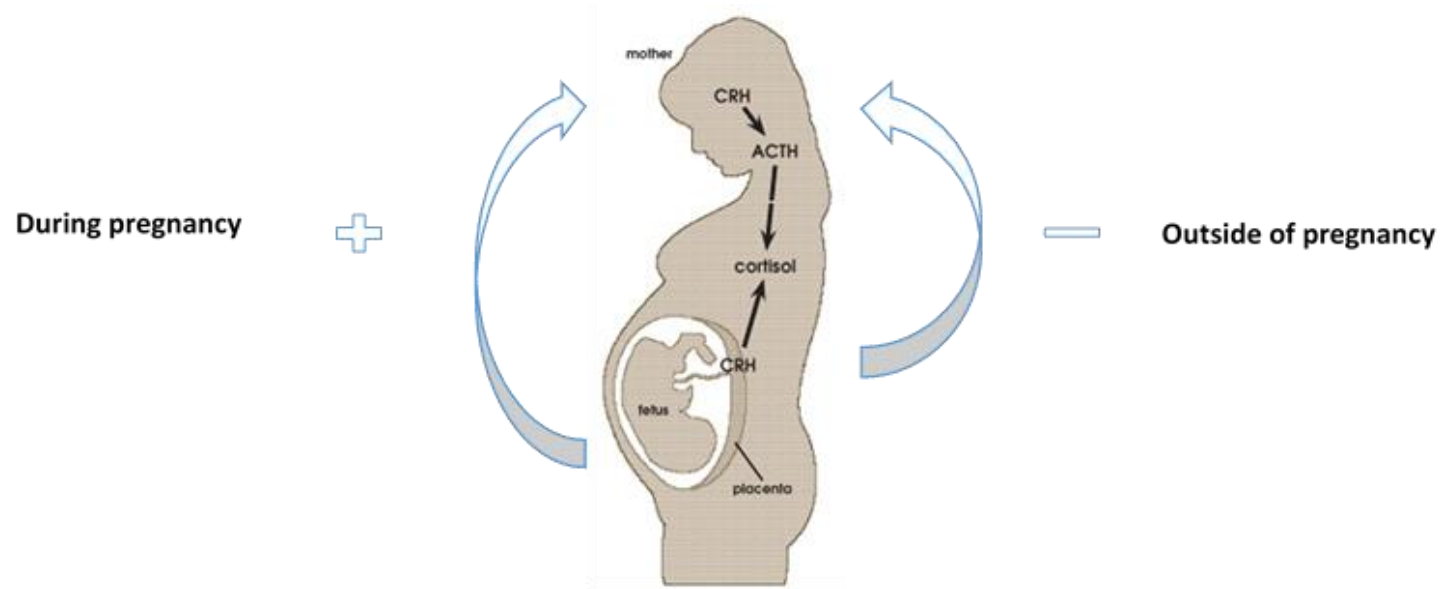


Figure 1.1: The maternal HPA axis during pregnancy: The release of CRH from the placenta creates a positive feedback loop, rather than the negative feedback loop characteristic of the HPA axis outside of pregnancy. Adapted from Glover and Kammerer (2004).

1.2.2 The hypothalamic pituitary adrenal axis and pregnancy

During pregnancy, the maternal HPA axis undergoes dramatic changes (Duthie & Reynolds, 2013). From approximately 25 weeks gestation, there is an exponential increase in a woman's basal cortisol as corticotrophin releasing hormone (CRH) is secreted from the placenta (Allolio, Hoffman, Linton, Winkelmann, Kusche et al. 1990). Rather than the negative feedback loop, characteristic of the HPA axis outside of pregnancy, placental CRH establishes a positive feedback loop over the course of gestation. This results in the simultaneous increase of CRH, adrenocorticotrophic hormone (ACTH) and cortisol within the maternal and fetal compartments (King, Smith & Nicholson 2001). Simultaneously, the placental enzyme 11 β -Hydroxysteroid dehydrogenase type 2 (11 β HSD-2) protects the fetus from exposure to the increasing levels of maternal cortisol by converting it to its inactive form, cortisone (Cottrell & Seckl, 2009). As term approaches (>36 weeks) maternal cortisol levels continue to increase while the expression of placental 11 β HSD-2 drops. This allows for a surge in glucocorticoid exposure to the fetus which accelerates fetal tissue maturation in preparation for birth (Xiong & Zhang, 2014).

1.2.3 HPA axis and Depression

The HPA axis has been implicated in the pathophysiology of a number of affective disorders (Keller et al., 2017). Abnormal patterns of cortisol secretion, such as hypercortisolemia or a flattened diurnal curve, are commonly observed in Major Depressive Disorder (Murphy, 1991; Deuschle et al., 1997). These alterations in HPA axis activity potentially occur as a consequence of impaired negative feedback within the HPA axis system or as a result of hypersecretion of CRH from the hypothalamus (Pruessner, Hellhammer, Pruessner & Lupien, 2003). Despite the dramatic alterations to the HPA axis, even greater HPA axis hyperactivity has been observed in pregnant

women with depression (O'Keane, Lightman, Marsh, Pawlby, Papadopoulos et al., 2011; Peer, Soares, Levitan, Streiner & Steiner, 2013; O'Connor, Tang, Gilchrist, Moynihan, Pressman et al., 2014). It has been theorised that exposure to these higher levels of circulating cortisol in depressed women can 'programme' fetal HPA axis development during gestation. Glover and colleagues (2009) have proposed that the enzyme 11 β HSD-2 becomes saturated in antenatal depression and is unable to convert cortisol to cortisone (Glover, Bergman, Sarkar, & O'Connor, 2009). A further theory proposes that affective symptoms in the mother may impair the function of 11 β HSD-2 resulting in an increased permeability of the placenta to cortisol across gestation (O'Donnell et al., 2012).

It is known that glucocorticoids play a key role in the 'programming' of the developing fetal brain. Exposure to excess glucocorticoids *in utero*, as a result of maternal antenatal depression is proposed to alter the development of the fetal HPA axis (Davis et al., 2007). Higher urinary cortisol levels and blunted cortisol response to a heel prick have been observed in newborn infants of mothers with antenatal depressive symptoms (Field, Diego, Dieter, Hernandez-Reif, Schanberg et al., 2004; Keenan, Gunthorpe & Grace, 2007). Higher antenatal cortisol has also been associated with higher basal cortisol and increased cortisol reactivity in infants of six months and five years of age (Brennan, Pargas, Walker, Green, Newport & Stowe, 2008; Gutteling, de Weerth & Buitelaar, 2005).

1.2.4 Genetic influences for perinatal depression and associations with fetal programming

It is widely understood that MDD in the general population has a strong genetic component with heritability rates of approximately 37-38% estimated from both meta-analyses and twin studies (Kendler, Gardner, Neale et al., 2006; Sullivan, Neale & Kendler, 2000). Studies investigating the genetic basis of depression have typically focused on the monoaminergic genes such as serotonin, dopamine and norepinephrine

and in recent years, several polymorphisms in these genes have been identified as contributing to MDD onset (Nutt, 2008; Corwin et al., 2010). Polymorphisms of the serotonin transporter, monoamine oxidase A, catechol-*O*-methyltransferase and the brain-derived-neurotrophic-factor (BDNF) gene have been specifically linked to depression in the postpartum period (Corwin et al., 2010). Overall, there is limited literature on the genetic basis of depression specifically within the perinatal period but existing data suggests that the heritable component may be greater than that of non-perinatal MDD (Murphy-Eberenz et al., 2006; Forty et al., 2006).

Currently, the genetic mechanisms underlying developmental programming are poorly understood. This is partly due to the difficulties in disentangling the effects of shared genes between mother and infant (Devlin et al., 2010; Braithwaite et al., 2014). However, it is suggested that the effects of heritable genetic variants may partly account for the associations between maternal stress and later child outcomes such as temperament and susceptibility to psychopathology later in life (O'Donnell & Meaney, 2017). Some studies, such as that of Smith (2008) have attempted to disentangle the influences of genes and the environment by comparing the strength of associations between infant outcomes and exposure to antenatal depression among mother-infant dyads compared with father-infant dyads. Using the same design as Smith (2008) above, Capron et al., (2015) reported an increased risk of anxiety disorders in adolescents exposed to maternal depression *in utero* with no evidence of increased risk following exposure to paternal depression or anxiety during pregnancy. These findings further support the evidence regarding the association between *in utero* fetal programming and the increased risk of later depression. However, until more is understood about the genetic processes underlying this association offspring vulnerability is still best described in terms of genetic predisposition and environmental risk (O'Donnell & Meaney, 2017).

1.2.5 Epigenetic alterations at the glucocorticoid receptor

There is accumulating evidence to support the role of glucocorticoids in fetal programming and recently, research in this area has shifted to focus on the role of glucocorticoids in epigenetic programming. Epigenetics is the study of the molecular modification of genes that does not involve changes to the underlying DNA sequence (Monk et al., 2012). The most widely investigated and understood epigenetic mechanism is that of DNA methylation, the process in which one of the four bases in DNA the cytosine nucleotides undergoes a process involving the addition of a methyl chemical group, which can lead to gene silencing (Razin, 1998).

In recent years, attention has focused on the epigenetics in the glucocorticoid receptor gene. The physiological actions of glucocorticoids are mediated by the glucocorticoid receptor (GR) due to the critical role that the GR plays in the negative feedback inhibition of the HPA axis (Oakly & Cidlowski, 2013). Increased DNA methylation within the NR3C1 gene, the gene that encodes for the glucocorticoid receptor, results in the decreased expression of glucocorticoid receptors within the hippocampus. This results of the dampening of the negative feedback response within the HPA axis and a prolonged increase in circulating glucocorticoids (Weaver et al., 2004). Oberlander et al (2008) reported that increased maternal depression symptoms in the third trimester were associated with increased methylation of the NR3C1 gene in neonatal cord blood. This increased methylation was also associated with increased HPA axis stress reactivity when the infants were three months old. Epigenetic modifications can also be inherited and are hypothesised to contribute to the heritability of depression and other affective disorders (Trerotola et al., 2015).

1.2.6 Maternal behaviour in pregnancy

In addition to the above neurobiological mechanisms that can alter fetal development, maternal health behaviours are also often impacted by antenatal depression. These behaviours can have a teratogenic effect on fetal development and can further

contribute to adverse infant outcomes. Antenatal depression is associated with a less healthy diet during pregnancy (Barker, Kirkham, Ng & Jensen, 2013) and increased rates of illicit drug use as well as alcohol and tobacco consumption (Le Strat, Dubertnet & Le Foll, 2011; Zhu & Valbo, 2002). Smoking during pregnancy can also reduce blood flow to the fetus, thus decreasing nutrient intake (Azar et al., 2010). Furthermore, ethanol easily crosses the placenta impacting cellular development of the fetus, disrupting hormonal interactions that occur between mother and fetus and consequently altering the development of neuroendocrine systems such as the HPA axis (Pearson et al., 2015; Weinberg et al., 2008).

1.2.7 Glucocorticoids as a mediator of infant and child outcomes

Exposure of the fetus to excess glucocorticoids *in utero* is typically cited as the primary pathway involved in ‘fetal programming’ and the proposed link between antenatal depression and infant outcomes in the postnatal period, later childhood and adulthood. Dysregulation of the HPA axis has been proposed to play a role in a number of adverse birth outcomes, particularly that of pre-term birth and low birth-weight. Women who deliver pre-term have both significantly elevated corticotropin releasing hormone (CRH) and an accelerated rate of CRH across gestation (Hobel et al., 1999; McGrath & Sullivan, 2002). Increased levels of cortisol *in utero* have also been proposed to restrict fetal growth by reducing blood flow to the placenta resulting in a restriction of oxygen and nutrients to the fetus and contributing to lower birthweight. This link between cortisol and lower birthweight is of particular importance due to the evidence also linking fetal growth with later psychopathology (Breslau & Chilcoat, 2000; Costello et al., 2007).

There have been some reported associations between maternal cortisol reactivity to stress during pregnancy and infant negative reactivity as well as crying and fussing behaviours (Bolten et al., 2013; Davis et al., 2007; De Weerth et al., 2003). However, several studies have also found no link between maternal antenatal cortisol and reports of infant temperament or the link exists only an indirect pathways through

infant birthweight (Baibazorova et al., 2013; Rothenberger et al., 2011). Additionally, aspects of neurodevelopment such as cognition and psychomotor development also have associations with antenatal cortisol. However, studies that have measured both antenatal depression and antenatal cortisol report that both of these variables are independent predictors of infant outcome rather than antenatal cortisol mediating the relationship between the two (Waters et al., 2014).

More recently, there have been investigations of the epigenetic alterations in the DNA methylation of NR3C1; the glucocorticoid receptor gene, as a potential candidate which may mediate the relationship between antenatal depression and infant behavioural and neurodevelopmental outcomes. Initial evidence has indicated antenatal depression and increased methylation in placental NR3C1 has been associated with poorer neonatal self-regulation, motor skills, attention skills and habituation to novel stimuli (Bromer et al., 2013; Appleton et al., 2015). In a further study, Parade et al (2016) reported that increased methylation of NR3C1 was associated with internalising behaviours, though not externalising behaviours, in children aged three to five years.

One of the most reliable predictors of increased NR3C1 methylation has been the exposure to early adverse experiences such as abuse or neglect during childhood (Farrell et al., 2018; McGowan et al., 2009; Perroud et al., 2011). As a result there has been an increased focus on the infant's early life environment particularly in the infant's interactions with their primary caregivers. However, within the literature investigating antenatal depression and the associated outcomes for infants, most studies fail to account for the mother's behaviour, her caregiving ability and the interactive relationship she has with her infant.

1.3 Early life programming and the role of maternal care

The field of early life programming has historically focused primarily on pregnancy and the potential programming effects that can occur within the intrauterine environment. However, the ontogeny of human brain development extends beyond the intrauterine environment into the postnatal period where the developing brain is still susceptible to 'programming' influences during this time (Buss et al., 2012). During the postnatal period these influences are primarily in the form of a mother's, or other primary caregiver's parenting behaviour and the environment they create for their infant. This next section will discuss the important aspects of maternal caregiving in the postnatal period and how these aspects of caregiving impact infant developmental outcome. The current research reporting on how depression during the postnatal period can impact maternal caregiving will be outlined, as well as a brief summary of the studies that have researched the impact of antenatal depression on the development of the emergent mother-infant relationship. Lastly, current evidence demonstrating how maternal caregiving can moderate the relationship between infant early physiological systems and resulting infant behaviour will be discussed. This last section will discuss the evidence for the 'programming' effect of maternal behaviour during the postpartum period and its potential to alter infant developmental trajectories throughout infancy and into later childhood and adulthood.

1.3.1 Maternal care in the postnatal environment

An infant's ability to respond to the surrounding environment develops within the context of the mother-infant relationship (Brazelton et al., 1974). Through their caregiving and interactive behaviours mothers serve as an external entity through which the infant learns to regulate their biological, emotional and behavioural systems (McKenna & Mosko, 1994). Outside the basic needs of protection and survival, the mother-infant relationship serves multiple functions for her baby.

In the early period after birth, neonatal behaviour is often uncoordinated and disorganised and a primary focus of the mother-infant relationship is to support the development of the infant's emotional regulation (Bornstein & Tamis-LeMonda, 1997). The Mutual Regulation Model of mother-infant interaction (MRM; Tronick & Gianino, 1986) outlines the process of how infants begin to develop the initial ability to regulate their inner emotional states during the first year of life. From birth, infants attempt to control disruptions to their emotional state by using 'self-directed' regulatory behaviours such as sucking, rocking or withdrawal, behaviours that can be exercised without the need for external support. Infants typically utilise these 'self-directed' behaviours to reduce engagement with their environment if it is overstimulating or distressing. However, an infant's self-directed behaviours are not sufficient to fully achieve the ability to self-regulate and infants must utilise additional regulatory capacities provided by the mother in order for their emotional regulation ability to mature and function appropriately. Mothers who are aware of their infant's attempts to self-regulate can support their infant in this process, for example, a mother may remove a noisy toy which she perceives is overstimulating for her infant. In this manner she provides a supportive environment which is adequately stimulating, but not overly so, in order to allow the infant to independently master this skill.

In addition to learning to regulate and cope with their inner emotional states, infants also need to engage and maintain their contact with their surrounding environment in order to learn to live within it. During interactions with their mothers or other primary caregivers, infants use 'other-directed' behaviours, such as smiling or fussing, in order to signal to the interactive partner that they should continue or change what they are doing. Mothers who can respond appropriately to these 'other-directed' behaviours allow the infant to develop and maintain well-regulated emotional states and to increase the infant's ability to engage with their external environment (Tronick & Gianino, 1986).

Maternal sensitivity is the term most often used within the literature to describe mothers who respond appropriately to their infants and provide their infants

or children with prompt care that relates to the child's needs at a given point in time (Ainsworth, Bell & Stayton, 1974). Sensitive mothers alter their behaviour in order to interact at their infant's current level of development and structure their interactions in order to facilitate infant self-efficacy, self-regulation and optimise development (Bigelow et al., 2010). Since Ainsworth's initial work, the definition of maternal sensitivity has been further expanded to encompass an additional number of maternal qualities. These include; maternal affect, timing, flexibility, acceptance, conflict negotiation, awareness of infant cues and appropriate responsiveness (Van Doesum et al, 2007). Indeed the term 'responsiveness' or 'maternal responsiveness' is often used interchangeably to describe the construct of maternal sensitivity (Shin et al., 2008). In addition, 'responsiveness' is also often used to describe the temporal contiguity of a mother's response. However, temporal contiguity is considered as just one aspect of maternal sensitivity, defined primarily by a mother's promptness or frequency of response to infant signals. In contrast to maternal sensitivity, or maternal responsiveness, temporal contiguity does not consider the quality of the response provided by the mother (Bohlin et al., 1989; De Wolff & van Ijzendoorn, 1997). A mother's responsiveness towards their infants is communicated primarily across three modalities; face, voice and touch (Ferber, Feldman & Makhoul, 2008). Maternal facial expressions specifically, are a core feature of a mother's behaviour that play an important role in the support of an infant's development in regulating their emotions.

1.3.2 Maternal-infant affective matching

As outlined in Tronick and Gianino's Mutual Regulation Model (Tronick & Gianino, 1986) infants learn to regulate their biological, emotional and behavioural systems within the context of the mother-infant relationship. Within the first year, a key aspect of this develops in the context of the coordinative processes such as synchrony and affective behavioural matching that occur within mother-infant interactions (Feldman, 2007). Behavioural state matching within an interaction occurs when both mother and infant

are in the same affective state at the same time. A greater degree of affective matching is typically an indicator of good quality dyadic interaction (Moore et al., 2004; Lowe et al., 2012). Affective synchrony is a similar concept to that of behavioural state matching but refers to the process through which the mother and infant match each other's positive affective states only (Feldman, 2003; 2007).

From birth, infants are both interested and motivated to communicate with their caregivers and others around them (Bornstein & Tamis-LeMonda, 1997). At approximately two months, gaze and non-distress vocalisations are the primary modalities that infants use to engage during interpersonal interactions (Feldman, 2007; Hsu & Fogel, 2003). At this age, infants can partake in mutual gaze and match their facial expressions to that of their caregiver or interactive partner (Feldman, 2007). In infants of this age, although affective matching can occur, matched positive affect is not frequently observed (Feldman et al., 1999). The capacity to share affect with an interactive partner emerges at approximately six months. It is at this point that social interactions become more mutual and, while engaged in an interaction, infants can learn to adapt to changes in the mother's behaviour (Feldman et al., 1996). As the infant develops across the first year, the ability to share positive affect increases (Feldman et al., 1999). However as the infant moves towards more frequent engagement with objects, the nature of the interactions between mother and infants changes, resulting in less shared positive affect and more shared neutral affect (Feldman et al., 1999).

The ability of a mother-infant dyad to match their affective behaviour has been implicated in a number of beneficial outcomes for the infant. Affective matching has been primarily associated with the development of infant emotional regulation and development (MacLean et al., 2014; Feldman et al., 1999; Gable & Isabella, 1992). However, increased levels of behavioural matching and synchrony have also been associated with better cognitive processing at six months (Thompson & Trevathan, 2008) and are predictive of visual IQ and language achievement at two years (Feldman et al., 1996; Nicely et al., 1999). Increased levels of shared positive affect or synchrony

are also associated with positive adjustment at school and better relationships with peers (Harrist et al., 1994; Kennedy & Bakeman, 1984).

1.3.3 Maternal vocalisation behaviour

A further crucial element of maternal behaviour that supports early infant development, is how a mother uses her voice while interacting with her infant. Maternal vocalisations towards her infant facilitate the mother-infant relationship and lay the foundation for infant self-regulatory capabilities as well as cognitive, social-emotional and particularly language development. A mother's speech towards her infant, often called 'Motherese' or Infant-Directed Speech, has specific structural characteristics and intonation cues guiding the infant's attention into the interaction and scaffolding her infant's sense of self-efficacy. This in turn sets the precedent for the infant's engagement with his or her environment. As outlined in the section above, a responsive mother can react to behaviours or overtures made by her infant in a contingent and prompt manner (Bornstein, Tamis-LeMonda, Hahn & Haynes, 2008). Mothers who are attuned and focused on their infant will express this through vocalisations that are immediate, are frequently imitative of their infant and elaborate on the infant experience (Murray et al., 1993).

Infant-directed speech, in comparison to adult-directed speech, is comprised of shorter utterances, more repetitions and more questions (Murray et al., 1993). In engaging with their infants, mothers also use a higher mean pitch, wider pitch range, prosodic repetition and exaggerated intonation (Fernald & Simon, 1984; Fernald, 1989). Maternal speech towards her infant focuses on the infant's experience of the interaction as well as encouraging engagement with their surroundings through the elaboration of infant action, the naming and labelling of objects and descriptions of the proximate environment (Cazden & Courtney, 1972; Bornstein et al., 1992; Murray et al., 1993). Additionally, a mother alters her vocalisations according to the age of her infant, engaging in more utterances, words and a richer vocabulary as the infant gets older

(Henning, Striano & Lieven, 2005). Furthermore, in order for a mother to support and facilitate her infant's communicative development, it is important that her infant-directed speech is contingent to her infant's behaviour (Huttenlocher, Haight, Bryk, Seltzer and Lyons, 1991).

A key aspect of social communication is the ability of a person to perceive contingencies within the environment (Nadel et al., 2005). Contingency can be defined as the behaviour of one participant that is predictable from that of the other participant (Harder et al., 2015). Infants have the ability to detect contingencies within their environment from as early as birth and are highly motivated to engage in a contingent manner with interactive partners (Tarabulsky, Tessier & Kappas, 1996; Gewirtz & Palaez-Nogueras, 1991). Infants engaged in a contingent interaction with a caregiver display higher levels of positive emotional expression (Harder et al., 2015). In contrast, violation of the contingent element of an interaction typically elicits distress in the infant. This is frequently observed in experimental situations such as the 'Still-Face' procedure; an experimental procedure where a mother maintains a non-engaging 'still' face while sitting face-to-face with her infant (Tronick et al., 1978). The detection and expectation of contingency allows the infant to identify temporal patterns in their environment, providing the basis for turn-taking with the infant's caregivers. The opportunity of an infant to partake in a communicative exchange also provides the foundation for processing social and cognitive information as well as fostering the development of the infant's sense of self-efficacy (Jaffe et al., 2001).

The ability of a mother to be prompt in responding to an infant's overtures is considered an important element of Ainsworth's definition of maternal sensitivity (Ainsworth et al., 1974). An important factor to consider within a maternal-infant interaction is the duration of time or the response latency that it takes for a mother to respond to her infant. Young infants are limited in their capacity to encode information and store it in memory, therefore in order for the infant to perceive a response as contingent, a mother's response to an infant behavioural overture must occur within a

limited timeframe (Harder et al., 2015). Within the literature, no consensus currently exists as to what the 'ideal' latency window is within an interaction. What is known is that a mother's response to her infant can change depending on the context and is dependent on the proximity of the child to the mother, the communicative modality used and the function that the mother's behaviour aims to serve (Keller et al., 1999). Van Egeren and colleagues (2001) reported that most maternal responses to their infants occurred within two seconds but that a response duration of up to three seconds could be considered as a contingent response in infants aged four months. This latency window seems to remain stable over the first year (Leyendecker et al., 1997).

Maternal response latency windows tend to be shortest for vocalisation to vocalisation responses and in responding to infant non-distress vocalisations it has been reported that mothers of three to four month olds tend to respond within one second (Van Egeren et al., 2001; Keller et al., 1999; Mastaka, 1993). Ramey & Ourth (1971) reported that infants of three, six and twelve months of age only increased their rate of vocalisation when mothers responded immediately, demonstrating no vocalisation increases when their mothers delayed their response to either three or six seconds. During vocal exchanges, pauses or responses exceeding three seconds may signal a period of disengagement (Stern & Gibbon, 1979).

1.3.4 The impact of postnatal depression on maternal caregiving ability

It is widely reported that one of the leading risk factors for postnatal depression is antenatal depression, particularly if depression in the antenatal period has gone undiagnosed or untreated (Leigh & Milgrom, 2008; Robertson et al., 2004) Although it is likely that gestational factors such as maternal health behaviours, exposure to excess glucocorticoids or epigenetic alterations may contribute some of the risks to offspring development, disruptions to maternal caregiving behaviour due to the onset of postnatal depression or as a result of continuing depressive symptoms from the

antenatal period also plays a significant role in infant and child outcomes (Kaplan et al., 2002). As highlighted in the above sections, an infant's early emotional regulation, cognitive and language development are fostered through their mother's use of positive affect, infant directed-speech and maternal responsiveness. Depressed mothers' behaviour has been reported to vary across these domains from mothers who are not depressed (Sohr-Preston & Scaramella, 2006).

Early studies, such as those carried out by Tiffany Field and Jeffrey Cohn in the late eighties and early nineties described the interaction styles of postnatally depressed mothers as falling into one of two categories; 'withdrawn' or 'intrusive' (Cohn et al., 1990; Field et al., 1996). Intrusive behaviour was used to describe behaviours exhibited by the mother that were overstimulating to her infant and consisted of behaviours such as rough tickling, poking and tugging at the infant. In contrast 'withdrawn' behaviour was under-stimulating to the infant and consisted of low levels of vocalising, reduced touching of the infant, and general disengagement during interactions and play (Field et al., 1990). However, these earlier studies with high-risk samples, were considerably flawed in their methodology and failed to control for psychosocial risk factors such as lower SES, education and young maternal age, variables which are all independent predictors of infant and child outcome (Rutter, 1974). More recent studies focusing on maternal-infant interaction have highlighted that such dichotomous behavioural styles are not as frequently observed in low risk samples, and that it is rare to observe intrusive behaviour within mother-infant interactions that are video-recorded for research purposes (Murray et al., 1996). However, these early studies laid the groundwork for studying the impact of maternal depression on mother-infant interactions outlining notable differences in the interaction behaviours of mothers with depression and their infants when compared with non-depressed mothers.

1.3.5 Postnatal depression and maternal affective expression

A mother's ability to match her infant's affective behaviour and achieve synchrony is an important element of maternal behaviour, particularly for supporting her infant's development of emotional regulation. The reported disruptions in the ability of infants born to mothers with antenatal and postnatal depression to regulate their emotional state is observed in their higher likelihood of displaying crying or fussing behaviours along with a more difficult temperament. Maternal display of affective behaviour has been of particular focus within the postnatal depression literature. Within dyadic interactions, mothers with depression have been reported to display negative affect more frequently (Field, Healy and LeBlanc, 1989; Field, Healy, Goldstein and Guthertz, 1990) and display less positive affect and less smiling (Paulson et al., 2009; Righetti-Veltima et al., 2002). In addition, mothers with depression match their infants' positive behaviour less often (Field et al., 1990). These difficulties in co-ordination of states are observed in both clinically diagnosed depression and in those mothers with sub-clinical symptomology (Weinberg & Tronick, 1998).

In non-clinical samples mother-infant interaction is not always smooth, synchronous or highly attuned. Across the first year, mothers and infants are typically co-ordinated for approximately one third of the time (Tronick & Cohn, 1989). However, in non-clinical samples, mismatches of affect or emotion are usually quickly repaired so that these mismatched states are of a short duration. It is proposed that mothers with depression have increased difficulty in reading their infants affective state and also have more difficulty with responding in an appropriate manner. This contributes to longer mismatches and fewer repairs within the interaction (Murray & Cooper, 1997; Tronick & Reck, 2009). Failure of a mother-infant dyad to achieve appropriate levels of affective matching can adversely the development of the infant's emotional regulation skills. Consequently, poor emotional regulation is seen as a precursor for the development of emotional difficulties later in life (Calkins & Fox, 2002).

1.3.6 Postnatal depression and maternal vocalisation behaviour

Maternal vocalisations towards her infant are recognised as one of the most important aspects of mother-infant interaction. A mother's infant-directed speech plays a crucial role in the infant's self-regulation, cognitive and language development. A number of elements of maternal speech behaviour have been reported to be impacted by depression. Mothers with depression express more negative affect in their speech as well as fewer explanations, suggestions and questions (Cox et al., 1987; Murray et al., 1993). Furthermore, the speech of mothers with depressive symptoms have longer and more variable switching pauses, defined as the duration of silence after the infant stops vocalising and the mother begins, and do not show shortened utterances for younger versus older infants. This highlights that depression can impair the ability of the mother to attune her infant-directed speech according to the infant's needs and appropriate developmental stage (Bettes, 1988; Zlochower & Cohn, 1996; Reissland, Shepherd and Herrera (2003). Lastly, during interactions with their infants, the speech content of mothers with depression tends to focus more on the mother's experience rather than that of the infant (Cox et al., 1987).

Maternal responsiveness or contingent responsiveness, referring to a mother's promptness or frequency of response to her infant rather than general maternal sensitivity, has surprisingly only been reported in a handful of papers in relation to postnatal depression. Mothers with depression have been reported to be slower to respond to their infant's vocalisations (Bettes, 1988) and show less contingent responsiveness to their infant's behaviour (Cohn et al., 1989). Beebe and colleagues (2008) reported that mothers with depression showed either high or low patterns of contingency across a number of modalities, a pattern that is potentially consistent with 'intrusive' or 'withdrawn' behaviour.

1.3.7 Antenatal depression and mother-infant interaction

The body of work investigating disruptions in postnatal maternal behaviour has primarily been discussed in the context of, or as a result of, postnatal depression. However, across the past decade several studies have emerged which have focused on the development of the mother-infant relationship within the antenatal period. This research has primarily focused on the maternal-fetal relationship or “the extent to which a woman engages in behaviours that represent an affiliation and interaction with their unborn child” (Cranley, 1981, p. 281). This relationship is an important part of maternal identity and plays a role in the positive adaptation of a woman to motherhood (Pisoni et al., 2014). In support of this, Alhusen, Hayat and Gross (2013) reported a link between the quality of the maternal-fetal relationship during pregnancy and the quality of the maternal-infant relationship in the postnatal period.

The development of the maternal-fetal relationship is also impacted by concurrent depression and it has been reported that women with a diagnosis of MDD during their pregnancy have lower emotional attachment to their developing fetus (McFarland et al, 2011). Pearson and colleagues (2012) proposed that depressive symptoms in mid-pregnancy may disrupt the initial development of responsiveness. They reported that antenatal depression was associated with a 30% increased risk of lower maternal responsiveness at twelve months postpartum. Thus experiencing depression during pregnancy can adversely impact the mother’s attachment or feelings towards her fetus, an effect which can carry over to the postnatal period and interfere with the early mother-infant relationship. Moreover, women with depressive symptoms during pregnancy speak, sing and read less to their fetus compared with controls (Hernandez-Reif et al., 2018), therefore it is possible that the impact of depression on maternal vocalisation behaviour towards her infant may have its origins in the antenatal period. However, the proposal that the development of maternal sensitivity or responsiveness can be impacted by depression during the antenatal period is still a relatively new idea and more research needs to be completed in this

area before any further conclusions can be reached as to whether this is indeed the case.

1.3.8 The moderating role of maternal caregiving on infant physiological and developmental outcomes

This current review of the literature has examined the developmental consequences of antenatal depression on the infant along with a summary of the biological mechanisms which are proposed to underlie these outcomes. Due to the high rates of continuity of depressive symptoms from the antenatal into the postnatal period it was important to take account of maternal behaviour in the context of postnatal depression also. Although the literature predominantly focuses on the adverse impact of postnatal depression on maternal behaviour, there have also been studies that have demonstrated no difference between the behaviour of mothers with depression in comparison with controls (e.g. Field et al., 1990; Weinberg et al., 2008). This is also an important factor to consider for both research and clinical practice as treatment that is successful in ameliorating a mother's symptoms during pregnancy means that her infant may never be exposed to alterations in maternal behaviour occurring as a result of postnatal depression. Numerous studies now indicate that the most important moderator between antenatal depression and infant and child outcomes is the nature and quality of parenting behaviour in early life (Stein et al., 2014). There is now a wealth of evidence that indicates that caregiving quality in the postnatal period can either ameliorate or exacerbate the effect of antenatal depression on infant outcomes providing evidence of the potential malleability in both infant behavioural and physiological systems (Van den Bergh, 2011).

Evidence for the moderation effect of early postnatal experiences on later biological and behavioural outcomes were first demonstrated in animal models using rats. Differing degrees of maternal care that mothers provided for their pups in the first

week following birth include licking and grooming (LG) and Arch-back Nursing (ABN), a behaviour where the mother actively encourages her pups to nurse, rather than passively letting them do so. High levels of both of these behaviours were noted to be associated with more positive offspring outcomes. Rat pups exposed to high levels of LG and ABN behaviours demonstrated lower glucocorticoid responses to stress (Liu et al., 1997). Moreover, rat pups with mothers who demonstrated low LG and ABN behaviours, representative of poorer caregiving, had increased methylation of the glucocorticoid receptor in the hippocampus, which in turn was related to higher offspring HPA axis activity (Weaver et al., 2004). The most notable aspect of this study was when the rat pups were cross-fostered from low LG and ABN mothers to high LG and ABN and vice-versa, they found that the methylation effects were reversed and that pups had a pattern of methylation related to their rearing mother, rather than their birth mother. This was the first study to demonstrate that maternal behaviours in the early days following birth can have lasting effects on gene expression and subsequent offspring stress reactivity (Sharp et al., 2012).

More recently, studies examining the moderating or mediating effect of maternal postnatal caregiving on infant physiological and behavioural outcomes in humans have also begun to emerge. Infants of more sensitive mothers, categorised according to the maternal behaviour Q-sort (Pederson et al., 1999), show greater cortisol variability across stress-eliciting challenges, reflective of an infant's ability to adapt to stressful situations (Atkinson et al., 2013). Furthermore Sheikh et al (2014) reported that greater parental positive affect during early caregiving moderated the effect of high cortisol reactivity on white matter fractional anisotropy (FA), a measure of connectivity in the brain obtained through diffusion tensor imaging (DTI). In this study 'high' stress reactive girls who received greater parent positive affect showed white matter structure more similar to that of 'low' stress reactive girls.

Recent studies have also demonstrated that fetal programming may also be modifiable through early postnatal experiences. Sharp et al (2012) attempted to replicate the findings reported by Weaver and colleagues (2004) in humans by investigating the effect of early maternal stroking on infant negative emotionality. They found that higher maternal depression scores during pregnancy were associated with increased infant negative emotionality only when mothers reported low maternal stroking. Bergman et al (2010) also reported a negative association between antenatal cortisol and cognitive development only in those children with an insecure attachment with their mother and not in infants with a secure attachment. Moreover Schechter et al (2017) reported that maternal antenatal distress predicted lower cognitive ability and that this relationship was strongest for children whose mothers exhibited low levels of positive engagement. These studies provide early evidence for the malleability of the stress response system in early infant life and indicate that adverse effects of exposure to adverse conditions *in utero* may potentially be reversed in the context of a supportive postnatal environment.

1.4 Aims and Structure of the thesis

This primary aim of this thesis is to investigate the relationship between antenatal depression and infant neuro-behavioural development across the first year of life. Studies investigating this aspect of infant outcome have primarily focused on children of school age and older have and reported inconsistent findings. A number of pathways are proposed to underlie the relationship between antenatal depression with infant outcome and two of these will be explored; the association between antenatal cortisol and infant neurodevelopment, a pathway implicated in fetal programming and the association between maternal antenatal and postnatal depression and maternal caregiving behaviours. Lastly, this thesis will explore whether maternal caregiving can

moderate the association between maternal antenatal cortisol and infant neurobehavioural and neurodevelopmental outcome.

Chapter 2 will describe the methodology used in this study, including the recruitment procedure and the measures used in the study. *Chapter 3* will address the association between antenatal depression and infant neurodevelopmental outcome across the first postnatal year. *Chapter 4* will evaluate the association between maternal HPA axis measures during pregnancy and infant neurodevelopment during the first year. *Chapter 5* will investigate the relationship between depression in both the antenatal and postnatal period and maternal interactive behaviour. *Chapter 6* will address the mediating or moderating role of maternal caregiving behaviour on infant neurodevelopmental outcome and finally, *Chapter 7* will discuss the overall findings of this study, outline potential directions for future aspects of research and discuss the strengths and limitations of the current study.

Chapter 2

Method

2.1. Study Design and overview

The studies in this thesis are part of the larger Perinatal REDEEM study (REsearch in Depression, Epigenetics, Endocrinology and NeuroiMaging). The study was funded by the Health Research Board (HRB) and the National Children's Research Centre (NCRC) to assess the impact of depression during pregnancy on infant HPA axis development, epigenetic mechanisms and neurodevelopmental outcome at 2, 6 and 12 months of age. This study was a prospective, longitudinal, observational study of pregnant women with a clinical diagnosis of depression, or a history of depression and non-depressed controls and their infants across the first year of life.

2.1.1 Contribution of work by the author

I was primarily responsible for data collection within the post-partum period. This involved the collection of behavioural data and biological samples. My primary role was to co-ordinate and complete the Neonatal Behavioural Assessment Scale (NBAS) assessments at 2 months and the Bayley assessments at 6 and 12 months. I collected all of the video recordings for the mother-infant interaction video-clips and distributed and collected the questionnaire data at each postpartum time point. Furthermore I was responsible for co-ordinating and collecting the infant saliva samples. I was aided in this task my colleague, who worked primarily on the pregnancy stage of the project, Dr. Chaitra Jairaj.

Dr. Jairaj (Research Registrar in Psychiatry) completed the initial work on this project including the completion of the ethics applications for all three hospitals, linking with the perinatal liaison psychiatry services in the NMH and the Coombe to set up clinics in order to recruit participants for the study. Both Dr. Jairaj and I jointly recruited the History and Control group from the antenatal booking clinics in the NMH.

Salivary cortisol analysis was completed by members of Professor Brian Keevil's laboratory at the University Hospital of South Manchester. Calculation of the cortisol parameters were completed by Dr. Jairaj. Four trained research assistants, Katie Moore, Britta Thiemt, Desiree Grafton-Clarke and Angana Nandy completed the coding for the video clips for maternal-infant interaction and the inter-rater reliability under the supervision of Dr. Jean Quigley and Dr. Elizabeth Nixon in the School of Psychology, Trinity College Dublin.

2.1.2 Ethical Considerations

Ethical approval for the study was granted from the research ethics committee within each of the three participating maternity hospitals in Dublin: the National Maternity Hospital (NMH), Holles Street, Dublin 2; the Coombe Women and Infants' University Hospital (CWIUH), Cork Street, Dublin 8 and the Rotunda Hospital (RH), Parnell Street, Dublin 1. All participants provided written consent for themselves and their infants.

2.2.1 Participants

2.2.2 Group Criteria

Participants were recruited into one of three groups based on the criteria outlined below:

- (i) Depressed group: a current diagnosis of an episode of Major Depressive Disorder (MDD) according to DSM-IV-TR criteria.
- (ii) History group: a previous history of one or more episodes of MDD but currently euthymic.
- (iii) Control group: no history of MDD or psychiatric disorder.

2.2.3 Inclusion and Exclusion Criteria

Pregnant women were considered for inclusion if they were in their second or third trimester of a singleton pregnancy and had a high level of both spoken and written English. Exclusion criteria for participation in the study were: women with obstetric complications, a chronic medical condition, a history or current diagnosis of an anxiety, psychotic, personality or substance abuse disorder and those taking medication, other than an antidepressant or mood stabiliser, on a long-term basis.

2.2.4 Participant Recruitment

MDD and MDD history groups

Participants in the depressed and history groups were recruited from the Perinatal Psychiatry services of the NMH and the CWIUH. All patients are referred to perinatal psychiatry through either their General Practitioner (GP) or by obstetricians or midwives in their respective maternity hospitals. Dr Chaitra Jairaj, a research registrar in Psychiatry, conducted clinics in the NMH and the CWIUH in order to recruit patients

for the study. Women who were referred to perinatal psychiatry for low mood or a history of low mood were triaged to Dr. Jairaj's clinics and were assessed and considered for eligibility for the study. Patients who currently met the criteria for Major Depressive Disorder or had a history of MDD but were currently euthymic were provided with a brief study information leaflet [Appendix i] with researcher contact details. Those women who were interested in participating at the time were provided with a more detailed explanation of the study, and a participant information leaflet [Appendix ii]. Following this all potential participants were offered the opportunity to ask any questions and it was reiterated that their decision of whether or not to participate in the study would not affect their care within the hospital. Patients who agreed to partake in the study signed a consent form to proceed with study participation [Appendix iii] and progressed with the recruitment procedure outlined in section 2.2.5 below. A number of participants who consented to take part in the study but due to time constraints were unable to complete the recruitment procedure during clinic hours. These participants were invited to return to either the hospital or Trinity College at a later date to complete the recruitment process then. Participants who were required to make a separate journey to participate in the intake interview were offered 30 euro as compensation for their travel expenses. All participants of the study received treatment as usual for their duration as a patient of the hospital. A small number of participants in the MDD History group were recruited through the antenatal booking clinics when, during the course of clinical assessment, they revealed a previous history of one or more episodes of MDD in their lifetime.

Control Group

Participants in the control group were recruited from the antenatal booking clinics within the three participating hospitals. Patients under 30 weeks gestation were approached and asked if they were interested in taking part in a research project that was ongoing within the hospital. If interested, patients were given a verbal summary of the study and were provided with a brief information flyer [Appendix i], as above. If

interested in participating, patients provided some brief contact details and were told that they would be contacted by Dr Jairaj to assess their eligibility for the study and discuss their participation in more detail. Control patients were contacted via phone or email within a week to confirm their interest in participating in the study. Those who were contactable and interested in participating were given a date for a recruitment interview and were emailed the detailed Participant Information Sheet [Appendix ii].

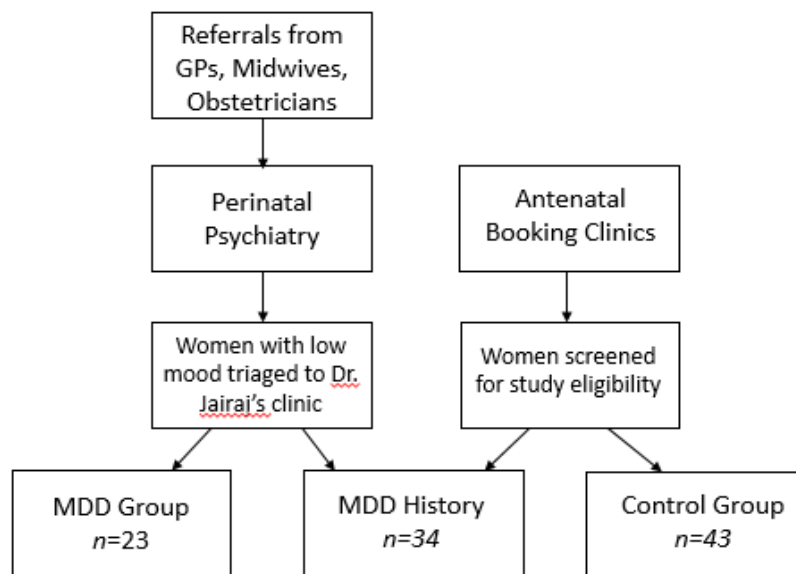


Figure 2.1: Flow Chart indicating the pathways through which participants were recruited to the study

2.2.5 Recruitment Procedure

Participants who were eligible to participate completed the procedure described below. All participants were provided with a study information leaflet and were also provided with an opportunity to ask questions or receive clarification on any details regarding their involvement in the study before agreeing to participate. Before participating, all patients signed a consent form (Appendix iii) to indicate their agreement to take part in the study. Following written consent, Dr. Jairaj completed a full diagnostic interview with each participant encompassing personal, family, medical, obstetric and psychiatric history in addition to current health and mental status. The clinician administered the

Mini International Neuropsychiatric Interview (MINI), which provided operational diagnoses for group inclusion and the Hamilton Depression rating scale (HAM-D) to determine an objective, continuous score of depressive symptomology. Afterwards, all participants completed four questionnaires: Center for Epidemiological Studies: Depression Scale (CES-D), the Perceived Stress Scale (PSS), the Pittsburgh Sleep Quality Index (PSQI) and the Childhood Trauma Questionnaire (CTQ).

2.2.6 Recruitment Challenges

Recruitment for the current study took place over 35 months from January 2014 to November 2016. Participant recruitment for all three groups was challenging due to a number of factors. The primary challenge was the duration of time that was required for the initial intake assessment. Approximately one hour per participant was required to explain the purpose and aims of the study, allow participant questions, complete a full clinical interview and adequate time in order to complete questionnaire measures. As all participants were recruited from psychiatry and antenatal booking clinics within the participating hospitals, time constraints often meant that Dr. Jairaj was unable to discuss the study in full detail with all potential participants at their scheduled hospital appointment time. Therefore it was necessary to contact the women outside of the clinic appointment and organise a further appointment for recruitment to the study. Attending a further appointment was a significant burden for all participants, particularly if they were currently employed or had other children to care for. As a result, a number of mothers were unable to return to the hospital or to Trinity College in order to complete the recruitment process.

A further challenge that arose during the recruitment process occurred in defining the History group during recruitment. It was difficult to ascertain whether previous episodes of depression were true episodes of clinical depression or whether they were periods of high levels of distress. During the recruitment interview, it was necessary to

ask participants to describe details of their past episodes of depression, which would have been subject to recall bias. Defining both the Depressed and Control was a more straightforward process as M.I.N.I and DSM-IV-TR criteria were used.

2.3 Measures

A summary of the measures collected for both mother and infant at each time point are outlined in Figure 2.2.

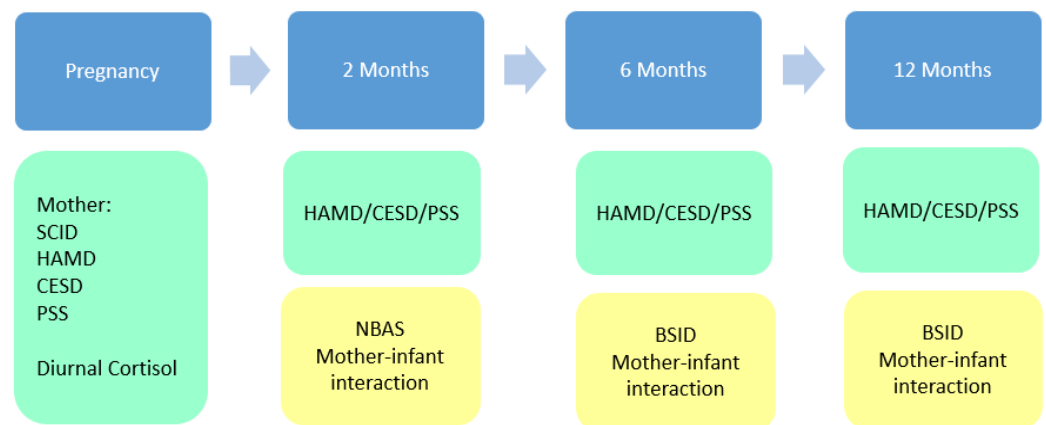


Figure 2.2 Overview of maternal and infant measures at each time point.

2.3.1 Demographic Characteristics

Maternal demographic information was recorded at the time of recruitment interview and included the following variables: maternal age, ethnicity, education, employment status and marital status.

2.3.2 Maternal health behaviours and obstetric factors

Maternal medication and current levels of cigarette and alcohol consumption were recorded. Maternal smoking and alcohol use were coded as nil or social use. Social use

was categorised as any smoking during pregnancy or, for alcohol, ≥ 2 units of alcohol use per week. Details pertaining to the mother's obstetric history and current pregnancy were also recorded. These variables included: pregnancy intent, gravidity, parity, and any previous obstetric complications.

2.3.3 Maternal Clinical Measures

MINI International Neuropsychiatric Interview (M.I.N.I.) (Sheehan et al., 1998)

The Mini-International Neuropsychiatric Interview (Appendix v) is a brief structured diagnostic interview for the major Axis I disorders in DSM-IV and ICD-10. The MINI consists of specific questions about psychological issues which require a yes or no answer. The MINI is divided into modules identified by letters, each corresponding to a diagnostic category. If a participant scores over a certain criteria they are considered to meet the diagnostic criteria for that category. For the purposes of this study, only the diagnostic categories pertaining to depression were used. These diagnostic categories were: A. Major Depressive Episode and Major Depressive Episode with Melancholic Features, B. Dysthymia and C. Suicidality. For the suicidality category, participants were assigned points depending on their responses to the questions asked. Questions associated with higher risk are weighted with higher points. This score was then categorised into 3 risk categories for current suicide risk: Low (1-8 points), Moderate (9-16 points) and high (≥ 17 points).

The MINI has a test-retest reliability of .78 and inter-rater reliability of .92. The MINI also has concurrent validity with the Structured Clinical Interview for DSM-III (SCID) .67 and the Composite International Diagnostic Interview (CIDI) .63

Hamilton Rating Scale for Depression (HAM-D) (Hamilton, 1960)

The HAM-D (Appendix vi) is a 21 item clinician rated measure of depression severity. It consists of 17 items relating to depressive symptoms such as mood, sleep, appetite and

suicide and a further 4 items which provide further information on depressive symptomology. Scores are based on the first 17 items and are measured on either a five point or three point scale which culminates in an overall score reflecting depression severity. Categories of depression severity are outlined in Table 2.2. Internal consistency for HAM-D-17 is .83 (Rush, Trivedi, Ibrahim et al., 2003)

Table 2.1: Categories of depression severity with corresponding HAM-D scores.

<i>Depression Severity</i>	<i>Score</i>
Normal	0-7
Mild Depression	8-13
Moderate Depression	14-18
Severe Depression	19-22
Very Severe Depression	≥23

Center for Epidemiologic Studies: Depression Scale (CES-D) (Radloff, 1977)

The CES-D scale (Appendix vii) is a 20-item self-report scale designed to measure current levels of depressive symptomatology. Participants are required to respond how often each item applied to them during the past week from a choice of (i) rarely or none of the time (less than 1 day), (ii) some or a little of the time (1-2 days), (iii) occasionally or a moderate amount of time (3-4 days) or (iv) most or all of the time (5-7 days). All items are scored on a basis of 0-3 points per item. Items 4, 8, 12 and 16 are inversely scored. The score attainable on the scale ranges from 0 to a maximum score of 60 with a higher score indicating greater depressive symptomatology. Although, not a clinical measure of depression, participants who score 16 or higher are identified as a depressive ‘case’ (Eaton et al., 2004). Internal consistency is excellent for the CES-D-20 ($\alpha=.88$), as is test-retest reliability (ICC=.87). Test-retest reliability for the individual items is poor to excellent (ICC=0.11-0.73) (La Chapelle & Alfano, 2005; Miller et al., 2008)

Perceived Stress Scale (PSS) (Cohen, Kamarck & Mermelstein, 1983)

The PSS (Appendix viii) is a 14 item self-report questionnaire designed to measure the degree to which situations in one's life are appraised as stressful. Participants are asked to indicate how often across the last month they felt or thought a certain way according to the statements provided. Participants can respond by answering (i) never, (ii) almost never, (iii) sometimes, (iv) fairly often or (v) very often. Each item is scored on a likert scale ranging from 0-4. Items 4-7, 9, 10 and 13 are positively stated items and are reversed scored. Internal consistency for the PSS-10 item scale is .89.

2.3.4 Infant Measures

A summary of the infant measures collected at each time point is presented in Table 2.1

Birth and Infant Characteristics

Infant birth details were obtained from participant medical records at each maternity hospital. In cases where these data were not available, the information was collected from the mother. Information on the mode of onset of labour, delivery method, infant gestational age at birth, weight at birth, 1 minute and 5 minute APGAR scores and head circumference were collected. Additional information on infant characteristics such as current weight, feeding method and hours of childcare per week were provided by the mother at the 2, 6 and 12 month time points.

Brazelton Neonatal Behavioural Assessment Scale-4th edition (NBAS) (Brazelton & Nugent, 2011).

The NBAS is an assessment of infant neurobehavioural development encompassing 28 behavioural items and 18 reflexes. These items are grouped into 'packages' which pertain to an established order across the domains of: habituation, motor-oral, truncal, vestibular and social-interaction (See Figure 2.1). Behavioural items are scored on a

scale of 1-9. (Appendix ix) During the course of the NBAS examination, particular focus is placed on the infant's state as infant reactions can be state dependent. Therefore, particular items can only be administered while the infant is in a specified state. For example: the habituation items are always carried out first while the infant is in a sleep state. If the infant is awake at the start of the assessment, this item is omitted. Likewise, the social-interaction package can only be administered when the infant is in an appropriate alert state. The NBAS was carried out in a quiet, semi darkened room, with a temperature of 22-27°C in either the mother's house or in a room with the same conditions within TCIN.

For scoring the NBAS, the six cluster scoring system by Lester, Brazelton & Als (1982) was used. Items were recoded according to the system outlined in Table 2.3. Mean values for each cluster were used as variables in the analysis along with the individual scores obtained for each of the supplementary items.

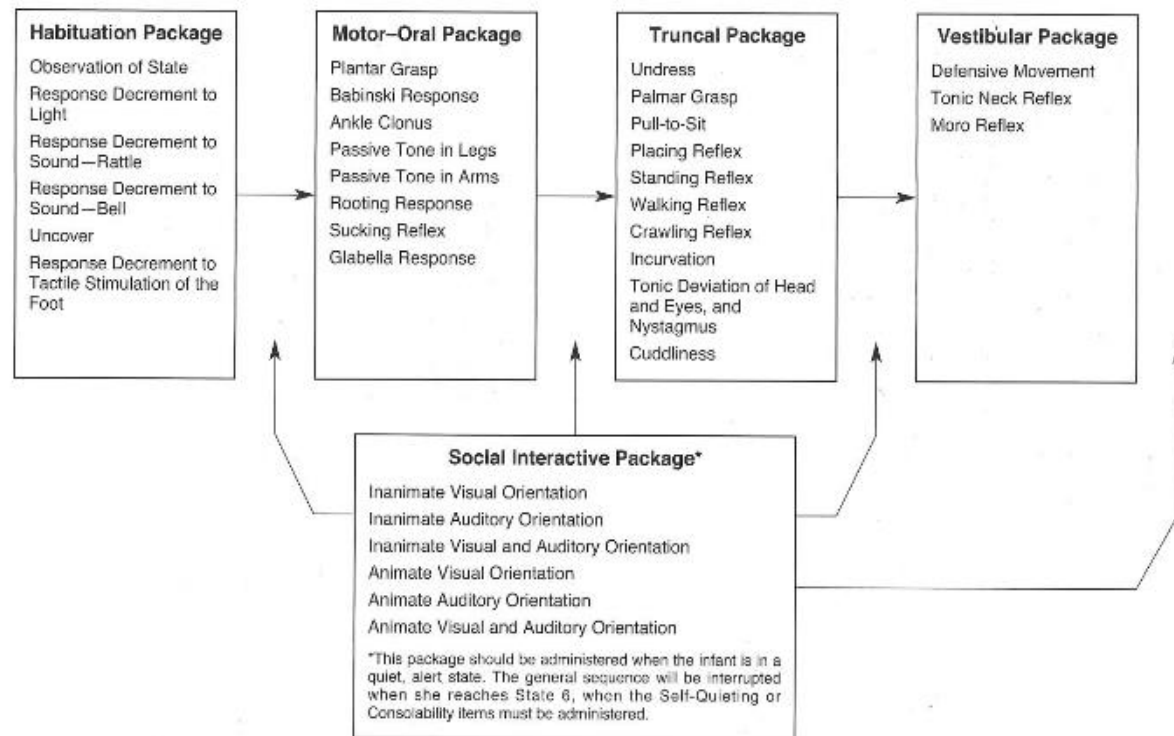


Figure 2.1: Administration sequence for the NBAS (from Brazelton & Nugent, 2011). For analysis, data were grouped using the cluster-scoring method outlined by Lester, Als and Brazelton (1982) into seven domains: Habituation, Orientation, Motor, Range of State, Regulation of State and Autonomic Stability. Lester et al's seven (1982) clusters are outlined in Table 3. In addition to these clusters, there are seven supplementary items which describes the infants overall performance over the course of the examination: Quality of Alertness, Cost of Attention, Examiner Facilitation, General Irritability, Robustness and Endurance, State Regulation and the Examiners Emotional Response. These items are not included in the cluster-scoring method and are assessed individually.

Table 2.2: NBAS seven cluster scoring criteria

BRAZELTON NEONATAL BEHAVIORAL ASSESSMENT SCALE SEVEN CLUSTER SCORING CRITERIA		
Items*		Clusters
		Habituation
1. Light.....	Raw score	
2. Rattle.....	Raw score	
3. Bell.....	Raw score	
4. Pinprick.....	Raw score	
		Orientation
5. Inanimate visual.....	Raw score	
6. Inanimate auditory.....	Raw score	
7. Animate visual.....	Raw score	
8. Animate auditory.....	Raw score	
9. Visual auditory.....	Raw score	
10. Alertness.....	Raw score	
		Motor
11. Tonus.....	Recode: 9/1 = 1; 8/2 = 2; 7/3 = 3; 4 = 4; 5 = 5; 6 = 6	
12. Maturity.....	Raw score	
13. Pull to sit.....	Raw score	
15. Defense.....	Raw score	
20. Activity.....	Recode: 9/1 = 1; 8/2 = 2; 7/3 = 3; 4/6 = 4; 5 = 5	
		Range of state
17. Peak of excitement.....	Recode: 9/1 = 1; 8/2 = 2; 4/3 = 3; 7/5 = 4; 6 = 5	
18. Rapidity of buildup.....	Recode: 9/1 = 1; 8/2 = 2; 7/3 = 3; 4 = 4; 5 = 5; 6 = 6	
19. Irritability.....	Recode: 9/1 = 1; 8 = 2; 7 = 3; 6 = 4; 5 = 5; 2,3,4 = 6	
24. Lability of state.....	Recode: 1,7,8,9 = 1; 5,6 = 2; 4 = 3; 3 = 4; 2 = 5	
		Regulation of state
14. Cuddliness.....	Raw score	
16. Consolability.....	Raw score	
25. Self-quieting.....	Raw score	
26. Hand to mouth.....	Raw score	
		Autonomic stability
21. Tremors.....	Recode: Invert: 9 = 1 (1 = 9); 8 = 2 (2 = 8); etc.	
22. Startles.....	Recode: If 1, drop; otherwise invert 2-9 on 8-point scale	
23. Skin color.....	Recode: 9,1 = 1; 8 = 2; 7 = 3; 6 = 4; 5 = 5; 3,4 = 6; 2 = 7	
		Reflexes
	An abnormal score is defined as 0, 1, or 3 for all reflexes except clonus, nystagmus, or TNR where 0, 1, and 2 are normal and 3 is abnormal. Reflex score = total number of abnormal reflex scores	
* Numbers represent Brazelton scale item number.		

* Numbers represent Brazelton scale item number.

Bayley Scale of Infant Development-3rd Edition (BSID-III) (Bayley, 2006)

Infants were assessed using the BSID-III at 6 and 12 months of age. The BSID-III is an individually administered instrument that assesses the developmental functioning of infants and young children aged 1 month to 42 months of age across three domains: cognitive, language and motor development. The BSID-III was administered in a quiet room in the mother's home according to standardised procedures outlined in the BSID-III manual. The BSID consists of five administered subtests: cognitive, receptive language, expressive language, fine motor and gross motor. Each infant receives a total raw score for each subtest of the BSID-III which is calculated by adding the total number

of items where the infant has received a score of 1 which includes all the items preceding the infant's baseline score. Raw scores are converted to norm-referenced scaled scores which represent the infant's performance on each subtest relative to their same age peers. Three composite scores; Cognitive, Language and Motor, are obtained from the scaled score of the cognitive subtest, the sum of the scaled scores for both the receptive and expressive language subtests and the fine and gross motor scaled scores. These composite scores are scaled to a metric with a range of 40 to 160, a mean of 100 and a standard deviation of 15. Reliability coefficients for the composite scales are excellent ranging from .91 (Cognitive) to .93 (Language) whereas subtest average reliability coefficients ranged from .86 (Fine Motor subtest) to .91 (Expressive Communication and Gross Motor subtests) (Albers & Grieve, 2007).

BSID-III Social-Emotional Scale (Greenspan, 2004)

The BSID Social-Emotional (SE) Scale is a 35 item questionnaire derived from the Greenspan Social-Emotional Growth Chart (Greenspan, 2004). This scale is completed by the mother and measures functional emotional skills including self-regulation, engagement with others, engagement with the surrounding environment, building relationships, communicating needs and the use of emotions and emotional signals. All items are tallied and this comprises the SE raw score. This score is then converted to a scaled score which accounts for age, using the appropriate table in the manual of the BSID-III. Internal consistency was estimated using coefficient alpha, with coefficients ranging from .83 to .94 for social-emotional items and .76 to .91 for the sensory processing items (Albers, 2007).

BSID-III Adaptive Behavior Scales (Harrison & Oakland, 2003)

The BSID Adaptive Behavior (AB) Scale is a 241-item questionnaire derived from the Parent/Primary Caregiver Form (for ages 0–5 years) of the Adaptive Behavior Assessment System-Second Edition (Harrison & Oakland, 2003). The items are

distributed across 10 different categories: *Communication, Community Use, Functional Pre-Academics, Home Living, Health and Safety, Leisure, Self-Care, Self-Direction, Social and Motor*. The *Community Use, Functional Pre-Academics and Home-Living* sections apply only to children over 1 year. These scales assess independence of daily living skills and are completed by the mother. The total score for each scale is tallied and converted to a General Adaptive Composite which provides an overall measure of adaptive development based on the 7 or 10 skill areas as applicable. Average reliability coefficients across each of the skill areas, adaptive domains, and the GAC ranged from .79 to .98. (Albers, 2007).

2.3.4 Biological Measures

Maternal Salivary Cortisol

Participants collected saliva samples during pregnancy and at the 2, 6 and 12 month time-points but only data obtained from the saliva samples collected during pregnancy were analysed for this thesis. Saliva samples were collected using Salivette™ swabs (Sarstedt). Mothers were asked to collect their saliva samples at 5 points across one day at the following times: Upon waking (0 minutes) and then 30 minutes, 60 minutes, 12 hours (720 minutes) and 12.5 hours (750 minutes) after waking. Participants were provided with written instructions (Appendix iv) and a demonstration on how to correctly use the saliva swabs.

At the pregnancy time-point, participants were asked to collect their saliva samples the day after the recruitment interview and were provided with a stamped envelope to return their samples to Trinity College. To minimise the time spent at room temperature, if the day of completion was on a Thursday or Friday, participants were asked to store their samples in their refrigerator and to place samples in the post on the following Monday. Salivary cortisol levels are stable at room temperature for up to

7 days and when refrigerated, for up to 3 months (Aardal & Holm, 1995; Garde & Hansen, 2005).

Saliva samples were centrifuged at 3500 rpm at 20°C for 15 minutes. Samples of 500µL of saliva were aliquoted into microtubes and stored at -80°C in Trinity College Institute of Neuroscience.

Calculation of the cortisol parameters were performed by Dr. Jairaj. All cortisol awakening response (CAR) parameters were calculated using data from the first three saliva collection time points: 0, 30 and 60 minutes after waking. The Area Under the Curve (AUC) with respect to ground (AUCg) and the AUC with respect to increase (AUCi) (Figure 2.2) were computed using formulae outlined by Fekedulegn and colleagues (2007). The parameters used for the study included:

The cortisol indices used for the study included:

- (i) *AUC with respect to ground (AUCg)*: is a variable that captures the total area under the curve where ground is equal to zero and is a measurement of total cortisol output.
- (ii) *AUC with respect to increase (AUCi)*: AUCi is a variable that captures the AUC with respect to increase from baseline and emphasises the change of cortisol over time.
- (iii) *Slope*: the slope of the regression line fitted through the morning time points
- (iv) *PM average*: The average of the two evening cortisol values.
- (v) *Diurnal Slope*: The slope of the regression line through the five time-points measured from waking to 12.5 hours post-waking.

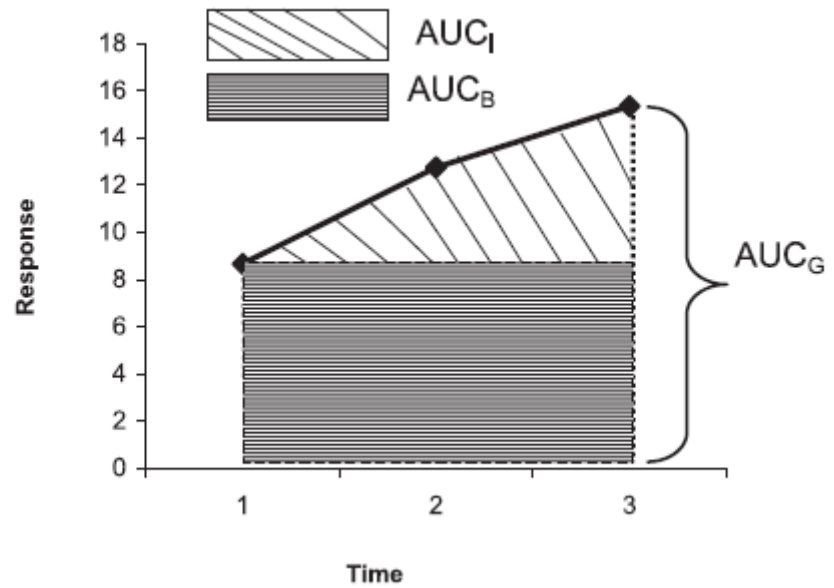


Figure 2. 2: Figure 2.4: Cortisol awakening response parameters: AUC_I and AUC_G adapted from Fekedulegn et al., (2007).

2.3.5 Maternal-Infant Interaction

Video Recordings

Following the completion of the developmental assessment at each time point a three minute video clip of a free play interaction between each mother and her infant was recorded using a NIKON D3100, a 14.2-megapixel DX format DSLR camera. Each mother was instructed to 'Play or interact with your baby as you usually would. You can use toys or not as you choose'. Mothers were allowed to choose how they would position their baby and what toys they would use, if any.

Affect

The videos were coded for affect by four coders who were completely blind to the purpose of the study. All coding was completed using INTERACT™ software (Mangold, 2006). Clips were coded for both maternal and infant moment to moment affective behaviour in separate phases. For both mother and infant, affective behaviour was

coded as either positive, neutral or negative using a coding system (Appendix x) which outlined behavioural signifiers for each classification of affective behaviour. This coding scheme was designed by the author along with Dr. Elizabeth Nixon and Dr. Jean Quigley of the School of Psychology, Trinity College. The proportion of time that mother and infant displayed either positive, neutral or negative affect was recorded as a percentage resulting in a possible six variables for each mother-infant dyad at two, six and twelve months. Four additional variables representing the proportion of time where mother and infant were matched for neutral, positive and negative affect and a composite variable comprising the total proportion of time that mothers and infants were matched for affect were also recorded. This variable was obtained through the co-occurrence function within INTERACT which searches for classes; situations where mother or infant are displaying positive, neutral or negative affect; that occur simultaneously for both mother and infant. INTERACT then calculates the total percentage of co-occurring events for each class separately. This comprises the variables of total matched neutral, negative or positive affect. These percentages were then added to create the percentage of time per clip that each dyad were matched for overall affect.

Maternal response latency and switching pause duration

The videos were coded for infant and maternal vocalisations by four coders who were completely blind to the purpose of the study. Coding for this variable was completed using INTERACT™ software (Mangold, 2006). In the first phase, any effortful or speech-like non-distress vocalisation made by the infant was coded. Infant sounds such as crying, fussing, laughing or other vegetative sounds were not coded. In the next phase any maternal vocalisations uttered within five seconds of the onset of an infant vocalisation were coded. Maternal sounds such as laughing or noises such as kisses or 'blowing raspberries' were not coded. Vocalisations made outside of the five second window were designated as a non-contingent vocal response. Two variables were obtained from these data: Mean response latency (RL) duration and Switching Pause

(SP) Duration. Mean maternal response latency for each participant was calculated by averaging the duration of time between the onset of the infant vocalisation and the onset of the mother's vocalisation. Switching pause duration was calculated by averaging the duration of time between the offset of an infant vocalisation and the onset of a maternal vocalisation for each participant. If the infant made no vocal overtures towards their mother during the three minute video-clip no data were coded for this clip. At two months there were no vocal overtures from eight of the infants [Depressed=1, History=3, Control=4], at six months there were no vocal overtures from two of the infants [Depressed=1, History=1] and furthermore at twelve months there were no vocal overtures from two of the infants [History=1, Control=1].

Maternal Mean Length of Utterance (MLU) and Lexical Diversity (vocd)

All maternal vocalisations observed in the video clips were transcribed by the author using CLAN (MacWhinney, 2000). Preliminary checks using the CHECK and MOR utilities were completed to ensure that the transcripts were set up correctly and to ensure that words were transcribed in the correct morphological structure. Two variables were obtained from the transcripts using the KIDEVAL utility within the CLAN program: Mean Length of Utterance (MLU) and Vocal Diversity (vocd).

Maternal Mean Length of Utterance (MLU) is a measure of maternal language complexity and is often used as a proxy measure of grammatical input (Sandbank & Yoder, 2016). MLU is denoted by the average number of morphemes per utterance of the mother during a sample of speech. *D (vocd*; Richards & Malvern, 2002) is a measure of vocal diversity which is based on the entire sample of words produced by the mother within a sample of speech. It is advantageous over other measures of vocal diversity such as the Type-Token Ratio, calculated by dividing the total number of unique words used by the total of words spoken, as it allows comparisons of speech samples of varying

sizes. Values for both MLU and *D* (vocd) were obtained from each transcript at two, six and twelve months.

Inter-Rater Reliability

Inter-rater reliability for the affect and vocalisation variables was completed by three research assistants who were completely blind to the purpose of the study. Inter-rater reliability was calculated for 16-26% of the video clips. Time-unit *Kappa* values reflecting the extent of agreement for positive, neutral and negative affect for both mother and infant are presented in Table 2.5. Percentage agreement for the mother-infant vocalisations are also presented in Table 2.5.

Interpretation of the value of *Kappa* is dependent on the number of categories that are coded. Within this study there were three potential categories in which affect was coded for both mother and infant; positive, neutral or negative, and whose frequencies were highly variable. Therefore kappa scores above; .83, .68, .55 represent observer reliability of 95%, 90% and 85% accuracy respectively (Bakeman and Quera, 2011).

Missing and Excluded Video Recordings

A number of mothers within this sample were not native English speakers and spoke to their infants in a language other than English. These clips were not transcribed and thus MLU or VOCD was not measured in these participants. In addition, a number of video clips are missing from the 2 month time-point for two reasons: (i) infants born in the initial part of the study did not partake in the developmental assessments as this arm of the study had not commenced yet and (ii) a number of infants were asleep at the time of the video recording. The participants for which interaction data were available is presented in Table 2.4.

Table 2.5: Number of mother-infant dyads for whom video-recordings were available for coding of Maternal Speech and Maternal-Infant affect at two, six and twelve months.

Time Point	Variable				
Maternal Speech (MLU, VOCD)					
	Depressed	History	Control	Non English	Total
2 Months	12	20	24	14	70
6 Months	18	22	30	17	87
12 months	16	23	32	15	86
Maternal-Infant Affect, Response Latency, Switching Pause					Total
2 Months	14	25	30	-	70*
6 Months	21	28	38	-	87
12 months	19	28	39	-	86**

*one video was not coded for affect

**seven videos not coded for maternal vocalisations

Table 2.6: Inter-rater reliability represented by time-unit Kappa values and percentage agreement at each time-point.

	Negative <i>kappa</i>	Neutral <i>kappa</i>	Positive <i>kappa</i>	Overall <i>kappa</i>	Affect % Agreement	Vocalisations % Agreement
Mother						
Two Months	n/a	0.39	0.62	0.31	67.53 %	90.65 %
Six Months	0.80	0.65	0.88	0.72	91.59 %	79.33 %
Twelve Months	n/a	0.62	0.80	0.61	85.49 %	85.47 %
Infant						
Two Months	0.64	0.65	0.55	0.55	75.55 %	92.61 %
Six Months	0.78	0.83	0.80	0.76	90.75 %	84.94 %
Twelve Months	0.80	0.79	0.67	0.69	85.86 %	88.76 %

2.4 Statistical Analyses

All data were analysed using SPSS (Version 24, IBM). Threshold of significance is set at 0.05 for all analyses. Data were assessed for normality using the Shapiro-Wilk test. Cortisol data was not normally distributed and was therefore log transformed in order to allow for analysis using general linear models. Due to the presence of positive skewness in the variables measuring affect, these variables were transformed using the ARCSINE transformation (Cohen & Cohen, 1983). Data that were not normally-distributed following transformation were analysed using non-parametric statistics.

Continuous data are presented as mean (M) and standard deviation (SD) and categorical data as percentage (%) and frequency. Standard error of the mean (SE) is presented in graphs. Box-plots represent the spread, median and interquartile range of scores for each group. Graphs were generated using GraphPad Prism Software Version 5 (GraphPad software Inc).

Data that were normally distributed data were analysed using Pearson's r correlations and general linear model analyses including: one way ANOVA, and linear or multiple regression as appropriate. The Tukey HSD test was used as in post-hoc analysis of group differences following ANOVA. Non-parametric data were analysed using the Kruskal-Wallis Test for Independent samples with post-hoc tests completed using Mann-Whitney U tests. Categorical variables were analysed using Pearson's Chi Square (χ^2) test and Fisher's Exact Test was used to analyse categorical data when the cell count was less than 5. For interpretation of the results of χ^2 test or Fisher exact test standardised residuals were examined. A standardised residual of ≤ 2 indicates that the observed frequency of a given variable is lower than the expected frequency. A residual of ≥ 2 indicates that the observed frequency is significantly higher than the expected frequency (Field, 2013). Non-parametric correlational analyses were conducted using Spearman's rank order correlations.

Mediation analysis was conducted using PROCESS, an SPSS macro (Hayes, 2013). PROCESS uses a regression based model to assess the relationship between a predictor variable and an outcome variable through their relationship to a third, mediating, variable (Field, 2013). A nonparametric bootstrapping method of 10000 samples and a confidence interval of 95% was used. An indirect association is considered to be significant if the 95% confidence interval does not include zero. Moderation analysis was also conducted using PROCESS (Hayes, 2013). For moderation analyses PROCESS uses a regression based model to test the combined effect of two variables, otherwise known as an interaction effect, on a third variable (Field, 2013).

2.5 Power Calculation

Post-hoc power analyses were calculated using G*Power (Faul, Erdfelder, Lang & Buchner, 2007) with power ($1-\beta$) set at 0.80 and $\alpha=.05$, two-tailed. Table 2.6 below outlines the sample size required for both group comparisons and continuous measure analyses in order to reach significance at the .05 level for each specified effect size.

Table 2.5: Sample size requirements for group and continuous analyses calculated post-hoc

<i>ANOVA, 3 groups,</i>			
Effect Size f	.01 (Small)	0.25 (Medium)	0.4 (Large)
Sample Size Required	1, 548	252	102
<i>Multiple Regression</i>			
Effect size f^2	0.02 (Small)	0.15 (Medium)	0.35 (Large)
Sample Size Required			
2 predictors	485	77	36
3 predictors	550	68	31

Chapter 3

Antenatal depression and infant
neurodevelopment in the first postnatal year

3.1 Introduction

The Developmental Origins of Health and Disease (DOHaD) hypothesis proposes that early life experiences, particularly within the intrauterine environment, play a role in an individual's health outcomes later in life (O'Donnell & Meaney, 2017). This theory has recently been applied to explain the fetal origins of mental health, proposing that the mother's emotional well-being during pregnancy may have a significant impact on the neurodevelopmental, behavioural, endocrine and emotional outcomes for the developing child (O'Donnell, Glover, Barker & O'Connor, 2014). Depression is estimated to impact 7-20% of women during pregnancy and is associated with a higher risk of adverse outcomes for both mother and infant such as pre-eclampsia (Kurki et al., 2000), increased risk of operative delivery (Chung et al., 2001) and lower gestational age and infant weight at birth (Grote et al., 2010).

Accumulating evidence suggests that antenatal depression is associated with adverse infant outcomes in the postnatal period as well as later in childhood (Eastwood et al., 2017). Within this literature the primary focus has been on investigating the links between antenatal exposure to maternal depression and the increased risk to the offspring for developing depression or other psychopathology later in life. To this end research has focused on the social-emotional aspects of infant and child development such as temperament and risk of behavioural issues or disorders in childhood (Stein et al., 2014). Many studies have neglected to focus on other aspects of infant outcome such as cognitive, language and psychomotor development. These aspects of development are strongly dependent on early experiences, frequently co-occur with behavioural and social-emotional issues and also have predictive value for the development of depression and other psychiatric disorders later in life (Bornstein et al., 2010; Gale et al., 2008).

3.1.1 Clinical diagnosis and self-report symptoms of mood.

Typically, studies investigating the impact of antenatal depression on maternal and offspring outcomes measure maternal depression at one point during pregnancy often using a self-report measure such as the Edinburgh Postnatal Depression Scale (EPDS; Cox et al., 1987), Beck Depression Inventory (BDI; Beck et al., 1996) or the Center for Epidemiological Studies Depression Scale (CESD; Radloff, 1977). Utilising a self-report measure on a once-off basis may indicate transient distress rather than enduring distress. Matthey and Ross-Hamid (2012) reported that within a sample of women who scored over 10 at first administration of the EPDS in the first trimester only half of these women had a similarly high score on this measure two weeks later. A clinical diagnosis of depression which considers the presence of persistent low mood and additional depressive symptoms for a period of two weeks or longer is more reflective of enduring distress which is likely to have a more significant impact on the developing fetus in comparison to transient distress.

3.1.2 Antenatal depression and infant neurobehavioural development in the early postpartum period.

Within the postnatal environment, there are a number of factors that can exert an independent influence on infant and child developmental outcomes such as maternal postnatal depression or caregiving ability. One method of researching the impact of antenatal depression on infant outcome while minimising the impact of the postnatal environment is to assess the infant as soon as possible after birth. The Brazelton Neonatal Behavioural Assessment Scale (NBAS) is the most commonly used instrument for assessing the neurobehavioral repertoire of infants and neonates. Utilising the NBAS, it has been reported that infants born to mothers with antenatal depression demonstrate increased fussing and crying behaviours (Diego et al., 2004), lower autonomic stability (Figueiredo et al., 2017; Goodman et al., 2011), lower habituation and motor scores (Field et al., 2001), lower state regulation (Goodman et al., 2011;

Hernandez-Reif et al., 2006) and lower orientation scores (Field et al., 2001; Hernandez-Reif et al., 2006) compared with control infants. Due to the timeframe within which these studies were carried out, 24 hours to 5 days post birth, it is suggested that differential infant behaviour is present at the earliest age, supporting a fetal programming hypothesis.

3.1.3 Antenatal depression and infant neurodevelopment within the first year and beyond

Currently, little is known about the impact of antenatal depression on neurodevelopment in later infancy and early childhood. To date, much of the research in this area has investigated neurodevelopment in school-aged children and older and these studies reveal inconsistent results varying from an increased risk of developmental delay, language disorder and a negative association with both cognitive and language development (Deave et al., 2008; Brown et al., 2016; Koutra et al., 2013; Schechter et al., 2017; Skurtveit et al., 2014; Evans et al., 2012) to no reported impact (Koutra et al., 2017; Tse et al., 2010; Hay et al., 2008; Maselko et al., 2015) or that negative associations hold only when mothers report both depression and anxiety symptoms (Ibanez et al., 2015). Additionally, positive associations between antenatal depressive symptoms and infant BSID scores at 24 months of age have also been reported (DiPietro et al., 2006). An extensive literature search revealed only two studies focusing on the impact of antenatal depression on infant cognitive, language and psychomotor outcomes within the first postnatal year. Bhang et al (2016) reported a negative association between first trimester depressive symptoms and motor development while Punamäki et al., (2006) reported no impact of second trimester antenatal depressive symptoms on infant developmental milestones at twelve months such as standing and words utterances.

3.1.4 Study outline

This study aimed to assess the impact of a clinical diagnosis of depression during pregnancy on infant neurodevelopment during the first postnatal year. Three groups of women were recruited to the study: a group of mothers who had a clinical diagnosis of Major Depressive Disorder (MDD) during pregnancy, a group of mothers with a history of one or episodes of MDD who were currently euthymic and a group of matched controls with no current psychiatric disorders and no history of depression. The inclusion of a History group is a novel aspect of this project and represents a group which is largely neglected in the research literature, despite being at the highest risk for developing depression across the perinatal period (Biaggi, Conroy, Pawlby & Pariante, 2015). This study employed a prospective longitudinal design and mothers were recruited into one of the above three groups during pregnancy and followed up at two, six and twelve months postpartum. At two months infant neurobehavioral development was measured using the Brazelton Neonatal Behavioural Assessment Scale (NBAS) and at six and twelve months the Bayley Scale of Infant Development (BSID) was used to assess infant cognitive, language and motor development. At all three time-points mothers also completed the social-emotional and adaptive behaviour questionnaires of the BSID.

Hypotheses

- 1) Infants born to mothers in the Depressed group would have lower scores on the NBAS compared with the Control group at two months.
- 2) Infants in the Depressed group would have lower scores on the cognitive, language and motor subscales of the BSID compared with the Control group at six and twelve months.

- 3) Infants in the Depressed group would have lower social-emotional and adaptive behaviour scores compared with Controls at two, six and twelve months.
- 4) There would be significant differences in the neurodevelopmental scores of infants born to mothers in the History group compared to the Depressed and Control groups at two, six and twelve months.

3.2 Method

3.2.1 Participants

Participants were recruited from the Perinatal Psychiatry services and antenatal booking clinics within the National Maternity Hospital, Holles Street the Coombe Women and Infants University Hospital and the Rotunda Hospital in Dublin. Participants who met the inclusion and exclusion criteria were clinically assessed by Dr Chaitra Jairaj, a research registrar in Psychiatry. Participants were recruited into one of three groups based on the criteria outlined below:

- (i) Depressed group: a current diagnosis of an episode of Major Depressive Disorder (MDD) according to DSM-IV-TR criteria.
- (ii) History group: a previous history of one or more episodes of MDD but currently euthymic.
- (iii) Control group: no history of MDD or psychiatric disorder.

3.2.2 Maternal Measures

Maternal Demographic Characteristics

Maternal demographic information was recorded at the time of recruitment interview and included the following variables: maternal age, ethnicity, education, employment status and marital status.

Maternal health behaviours and obstetric factors

Maternal medication and current levels of cigarette and alcohol consumption were recorded. Details pertaining to the mother's obstetric history and current pregnancy were also recorded. These variables included: gravidity, parity, and any previous obstetric complications.

Maternal Clinical Measures

The MINI International Neuropsychiatric Interview (M.I.N.I.) (Sheehan et al., 1998) and the Hamilton Rating Scale for Depression (HAM-D) (Hamilton, 1960) were completed by Dr Chaitra Jairaj at recruitment. Mothers also completed the Center for Epidemiologic Studies: Depression Scale (CES-D) (Radloff, 1977) and Perceived Stress Scale (PSS) (Cohen, Kamarck & Mermelstein, 1983) on recruitment to the study and at 2, 6 and 12 months postpartum. Details of these measures have been outlined in Chapter 2.

3.2.3 Infant Measures

Infant Birth Characteristics

Infant birth details were obtained from participant medical records at each maternity hospital. In cases where these data were not available, the information was collected from the mother. Information on the mode of onset of labour, delivery method, infant gestational age at birth, weight at birth, 1 minute and 5 minute APGAR scores and head circumference were collected. Additional information on infant characteristics such as current weight, feeding method and hours of childcare per week were provided by the mother at the two, six and twelve month time points.

Brazelton Neonatal Behavioural Assessment Scale-4th edition (NBAS) (Brazelton & Nugent, 2011).

The NBAS was carried out in a quiet, semi darkened room, with a temperature of 22-27°C in either the mother's house or in a room with the same conditions within TCIN and where possible when the infant was 8 weeks old. Mean infant age at assessment was 8 weeks, 1 day (Range: 7 weeks to 10 weeks 4 days). For analysis, data was grouped using the cluster-scoring method outlined by Lester, Als and Brazelton (1982) into seven

domains: Habituation, Orientation, Motor, Range of State, Regulation of State, Autonomic Stability and Reflexes. In addition to these clusters, there are seven supplementary items that describe the infants overall performance over the course of the examination: Quality of Alertness, Cost of Attention, Examiner Facilitation, General Irritability, Robustness and Endurance, State Regulation, Examiner's Emotional Response. Both the NBAS clusters and the supplementary items of the scale are outlined in further detail in Chapter 2. NBAS data is available for 72 of the infants within this study.

Bayley Scale of Infant Development-3rd Edition (BSID-III) (Bayley, 2006)

Infants were assessed using the BSID-III at 6 and 12 months of age. The BSID consists of five administered subtests: cognitive, receptive language, expressive language, fine motor and gross motor. Raw scores are converted to scaled scores, which account for age, using the appropriate table in the manual of the BSID-III. Three composite scores; Cognitive, Language and Motor, are obtained from the scaled score of the cognitive subtest, the sum of the scaled scores for both the receptive and expressive language subtests and the sum of the fine and gross motor scaled scores respectively. At the 6 month time point, the mean age at testing was 6 months 13 days (Range: 5m 29 days to 7m 17 days). At the twelve month time point the mean age at testing was 12 months 19 days (Range: 12m 0 days to 14m 2 days).

BSID-III Social-Emotional Scale (Greenspan, 2004)

The BSID Social-Emotional (SE) was completed by the mother at the 2, 6 and 12 month time points. All items are tallied and this comprises the SE raw score. This score is then converted to a scaled score and then to a composite score. The composite score for this measure is used for the purposes of the analysis.

The Adaptive Behaviour Scales were completed by the mother at the 2, 6 and 12 month time points. The total score for each scale is tallied and converted to a General Adaptive Composite. The composite score for this measure is used for the purposes of the analysis.

3.2.4 Statistical Analyses

Continuous data are presented as mean (M) and standard deviation (SD) and categorical data as percentage (%) and frequency. Standard error of the mean (SE) is presented in graphs. Box-plots represent the spread, median and interquartile range of scores for each group. Data were assessed for normality using the Shapiro-Wilk test. Normally distributed data were analysed using one way ANOVA or linear regression as appropriate. Non-parametric data were analysed using the Kruskal-Wallis Test for Independent samples and post-hoc tests were carried out using Mann-Whitney U tests. Categorical variables were analysed using Pearson's Chi Square (χ^2) test. Fisher's Exact Test was used to analyse categorical data when the cell count was less than 5. For interpretation of the results of χ^2 test or Fisher exact test standardised residuals were examined. A standardised residual of ≤ 2 indicates that the observed frequency of a given variable is lower than the expected frequency. A residual of ≥ 2 indicates that the observed frequency is significantly higher than the expected frequency (Field, 2013).

Maternal education, parity and infant sex were chosen as covariates for the data analysis. Parity was chosen as preliminary correlational analyses indicated an association between maternal parity and infant cognitive and language development at six months. Moreover both maternal education and parity are known to be independent predictors of infant neurodevelopmental outcome within the literature (e.g. Quevedo et al., 2012; Jedrychowski et al., 2009). Infant sex was chosen as numerous studies have reported that antenatal depression exerts differing effects on male versus female fetuses *in utero* (e.g. Wen et al., 2017; Quarini et al. 2016).

Multivariate linear regression analyses were used to test for significant differences between the Depressed, History and Control groups on each subscale of the BSID at six and twelve months. Dummy variables were coded for all three groups in order to enter them into the model as predictors. In the first analysis, dummy variables representing the Depressed and History groups were entered into the model with the Control group acting as the reference condition. In order to compare the Depressed and History group with each other, the Depressed group was used as the reference condition in a second analysis. For each subscale of the BSID, both analyses were conducted using three different models. Model 1 evaluated group comparisons with no adjustments for covariates. Model 2 evaluated group comparisons adjusting for parity, maternal education and infant sex. Model 3 evaluated group comparisons adjusting for parity, maternal education, infant sex and the current maternal CESD score, measured at 6 or 12 months. All statistical analyses were considered significant when $p < .05$. All data were analysed using SPSS (Version 24, IBM).

3.3. Results

3.3.1 Flow of participants

Figure 3.1 demonstrates the flow of participants within the study. One hundred participants were recruited into three study groups: Depressed ($n=23$), History ($n=34$) and Control ($n=43$). Eighty-seven mother-infant dyads remained in the study at twelve months resulting in an overall attrition rate of 13%. Attrition was equivalent across groups: Depressed ($n=4$), History group ($n=5$) and Controls ($n=4$). Reasons for non-completion of the study are outlined in Figure 3.1. Two participants were excluded at birth as one infant from the History group was diagnosed with Apert syndrome and one infant from the Control group was born pre-term at 27 weeks gestation.

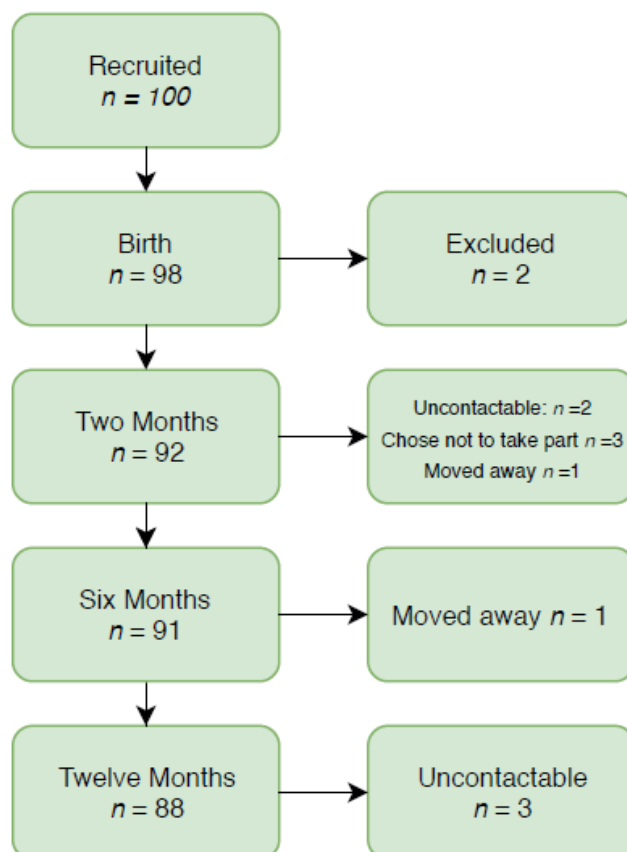


Figure 3.1: Flow chart of study sample

3.3.2 Demographic Characteristics

Maternal demographic characteristics are summarised in Table 3.1. There were significant differences between the groups for employment [Fisher Exact Test, $p=.006$] with more than expected women in the History group currently not in employment (standardised residual: 2.1). There were no significant differences between the Depressed, History and Control groups for maternal age, gestation, education, relationship status or ethnicity.

Table 3.1: Demographic characteristics of the sample

Variables	Depressed ($n=23$)	History ($n=34$)	Control ($n=43$)
Age (m, SD)	31.61 (3.88)	32.44 (5.24)	33.91 (4.73)
Gestation at recruitment (m, SD)	25.35 (4.75)	26.35 (2.92)	26.63 (3.98)
Education (n , %)			
Primary	-	-	-
Lower Secondary	1 (4.3%)	3 (8.8%)	-
Higher Secondary	2 (8.7%)	4 (11.8%)	1 (2.3%)
Post Secondary non-tertiary	4 (17.4%)	2 (5.9%)	7 (16.3%)
Third Level degree (non-honours)	-	2 (5.9%)	-
Third Level Degree (honours or above)	15 (65.2%)	22 (64.7%)	35 (81.4%)
Other/not stated.	1 (4.3%)	1 (2.9%)	-
Relationship Status (n , %)			
Single	2 (8.7%)	2 (5.9%)	3 (7%)
Cohabiting	10 (43.5%)	8 (23.5%)	12 (27.9%)
Married	11 (47.8%)	24 (70.6%)	28 (65.1%)
Employed (n , %)	18 (78.3%)	21 (63.6%)**	40 (93%)
Ethnicity			
Anglo-Saxon	22 (95.7%)	32 (94.1%)	38 (88.4%)
African	1 (4.3%)	2 (5.9%)	1 (2.3%)
South Asian	-	-	3 (7%)
Hispanic	-	-	1 (2.3%)

Comparisons are made with control group, **<.01

3.3.3 Health Characteristics

Maternal health characteristics are summarised in Table 3.2. There were significant differences between both the Depressed and Control groups and the History and Control groups for antidepressant medication use during pregnancy [$p < .001$, Fisher Exact Test]. Ten women in the depressed group and ten women in the History group were prescribed with antidepressant medication during their pregnancy.

Table 3.2: Health characteristics of the sample

Variables	Depressed (n=23)	History (n=34)	Control (n=43)
Parity (n, %)			
Nulliparous	12 (52.2%)	8 (23.5%)	21 (48.8%)
Primiparous	7 (30.4%)	17 (50%)	16 (37.2%)
Multiparous	4 (17.4%)	9 (26.4%)	6 (14%)
During pregnancy (n, %)			
Smoking	2 (8.7%)	3 (8.8%)	1 (2.3%)
Alcohol	-	7 (20.6%)	9 (20.9%)
Psychotropic Medication	10 (43.5%)	10 (29.4%)	-

3.3.4 Maternal Measures of mood during pregnancy and postpartum

Table 3.3 represents the mean scores for the Hamilton Rating Scale for Depression (HAM-D), Center for Epidemiological Studies Depression (CESD) Scale and the Perceived Stress Scale (PSS) for all time points. Box-plots representing the spread of scores along with the median and interquartile range are presented for all four time-points for the HAM-D (Fig 3.2), CESD (Fig 3.3) and the PSS (Fig 3.4). The plotted score trajectories for each group for each measure are presented in Figure 3.5, Figure 3.6 and Figure 3.7 respectively.

Hamilton Rating Scale for Depression (HAM-D)

Mothers in the Depressed group had significantly higher HAM-D scores compared with mothers in the History and Control groups during pregnancy and at two, six and twelve months postpartum. Mothers in the History group also had significantly higher HAM-D scores compared to mothers in the Control group during pregnancy and at two months. There were no significant differences between the History and Control group for HAMD scores at six and twelve months.

Center for Epidemiological Studies Depression (CESD) Scale

Mothers in the Depressed group had significantly higher CESD scores compared to the History and Control groups during pregnancy and at two, six and twelve months. Mothers in the History group also had significantly higher CESD scores compared to Controls during pregnancy and at two and six months postpartum. There were no differences for CESD scores between the History and Control groups at twelve months.

Perceived Stress Scale (PSS)

The Depressed group had significantly higher PSS scores compared to Controls during pregnancy and at two months, six months and twelve months postpartum. PSS scores for the Depressed group were also significantly higher in comparison with the History group during pregnancy and at six and twelve months. However at two months there were no differences between the depression scores for the Depressed or History groups. The History group had significantly higher PSS scores for the pregnancy, two and six month time-points. However at twelve months there were no significant differences between the History and Control group for PSS scores.

Table 3.3: Mean scores for the measures of maternal mood during pregnancy and postpartum

	Depressed (n=23)		History (n=34)		Control (n=43)		
Measure	Mean	(SD)	Mean	(SD)	Mean	(SD)	Statistic, p value
HAM-D							
Pregnancy	20.82	(5.01)	3.48	(4.3)	1.44	(1.6)	$\chi^2(2, 98)=55.81, p<.001^{abc}$
2 months	7.56	(6.60)	2.90	(2.51)	1.60	(1.5)	$\chi^2(2, 69)=15.443, p<.001^{abc}$
6 months	8.13	(8.14)	2.18	(1.83)	1.5	(1.1)	$\chi^2(2, 42)=7.268, p=.026^{ab}$
12 months	6.29	(4.64)	2.31	(2.5)	1.93	(1.98)	$\chi^2(2, 35)=6.668, p=.036^{ab}$
CES-D							
Pregnancy	35.55	(12.28)	13.62	(8.7)	6.38	(5.75)	$\chi^2(2, 96)=49.907, p<.001^{abc}$
2 months	22.36	(13.91)	13.07	(11.48)	6.53	(6.31)	$\chi^2(2, 78)=19.458, p<.001^{abc}$
6 months	25.08	(12.75)	12.48	(11.72)	6.08	(6.52)	$\chi^2(2, 72)=22.315, p<.001^{abc}$
12 months	21.50	(12.63)	12.88	(10.21)	8.86	(7.36)	$\chi^2(2, 79)=14.756, p<.001^{ab}$
PSS							
Pregnancy	36.68	(5.19)	24.06	(7.74)	17.14	(7.23)	$F(2, 92)=50.05, p<.001^{abc}$
2 months	29.86	(9.85)	24.14	(9.09)	17.81	(7.41)	$F(2, 76)=11.387, p<.001^{ac}$
6 months	31.33	(10.54)	23.08	(10.63)	17.06	(8.11)	$F(2, 70)=11.983, p<.001^{abc}$
12 months	30.56	(9.63)	23.58	(8.02)	20.86	(6.84)	$F(2, 76)=8.524, p<.001^{ab}$

HAM-D: Hamilton Rating Scale for Depression, CES-D: Center for Epidemiological Studies: Depression Scale, PSS: Perceived Stress Scale (Indicate that there are differences with the depressed. Significant group differences: ^adepressed vs control ^bdepressed vs history ^chistory vs control.

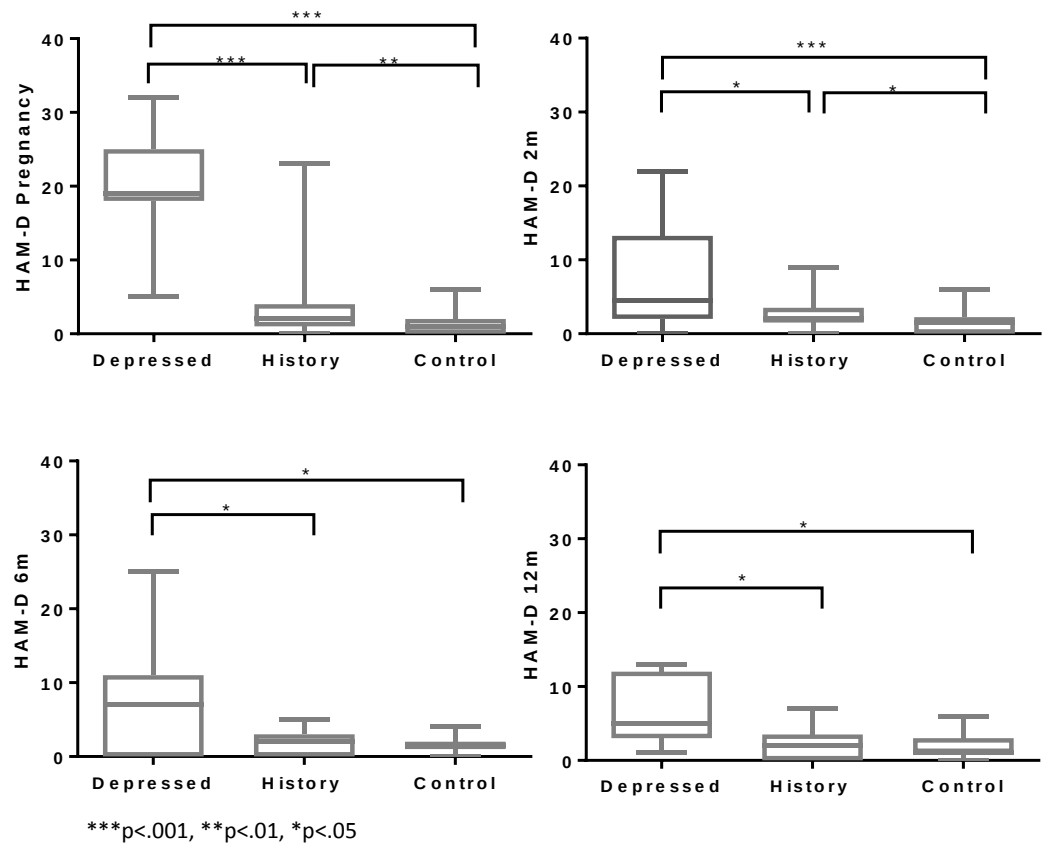
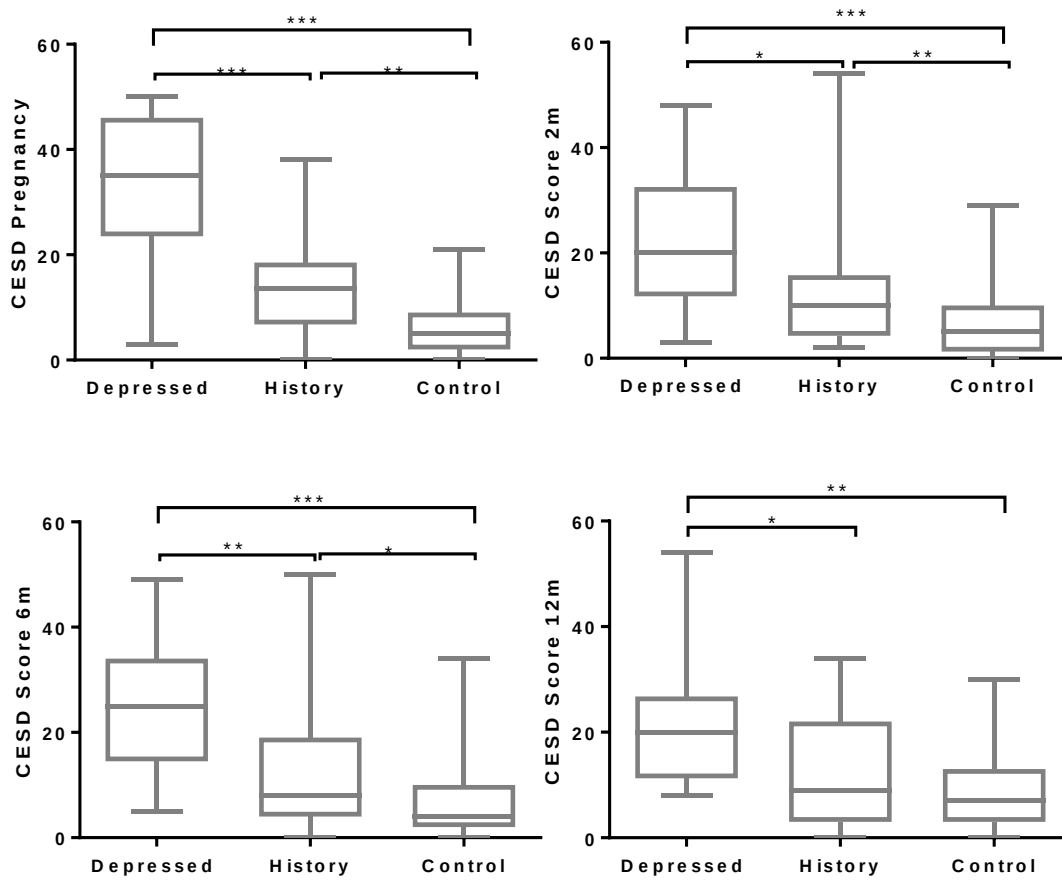
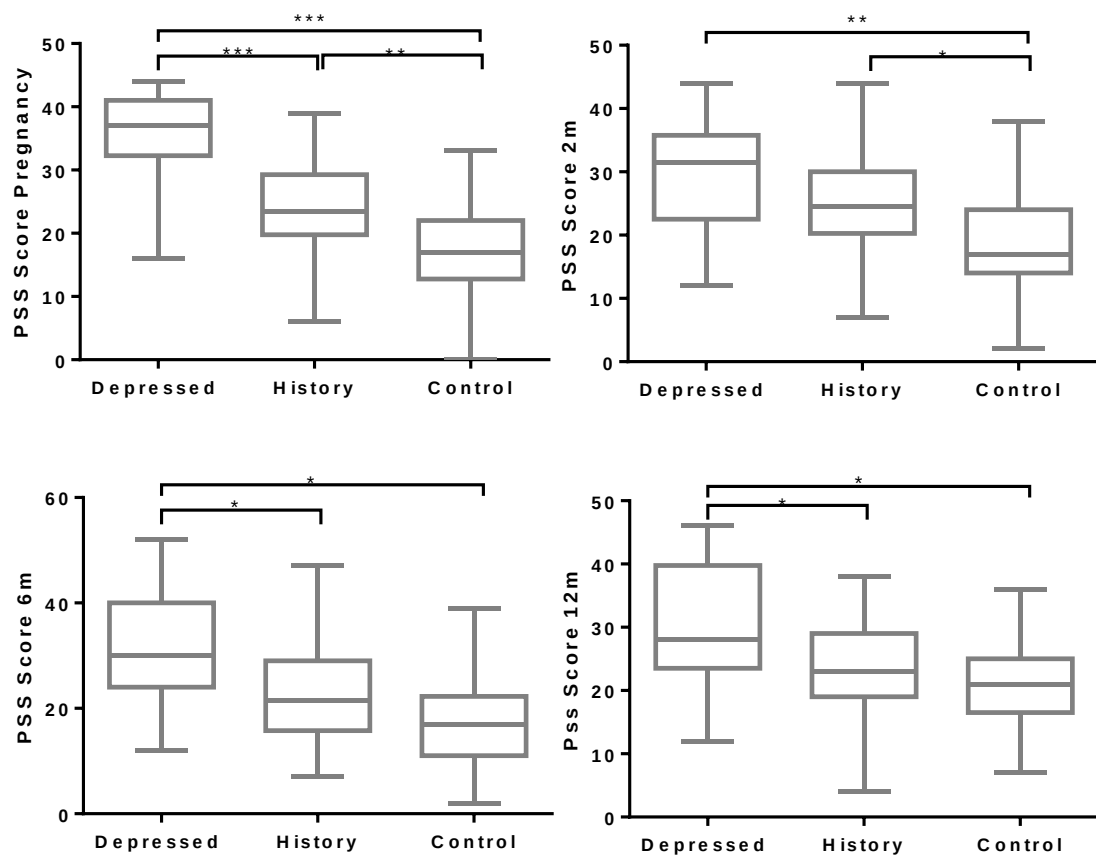


Figure 3.3: Hamilton Rating Scale for Depression (HAM-D) scores for the depressed, history and control groups during pregnancy, two, six and twelve months



*** $p < .001$, ** $p < .01$, * $p < .05$

Figure 3.4: Center for Epidemiological Studies: Depression (CESD) Scale scores for the depressed, history and control groups during pregnancy, two, six and twelve months.



*** $p < .001$, ** $p < .01$, * $p < .05$

Figure 3.4: Perceived Stress Scale scores for the depressed, history and control groups during pregnancy, two, six and twelve months.

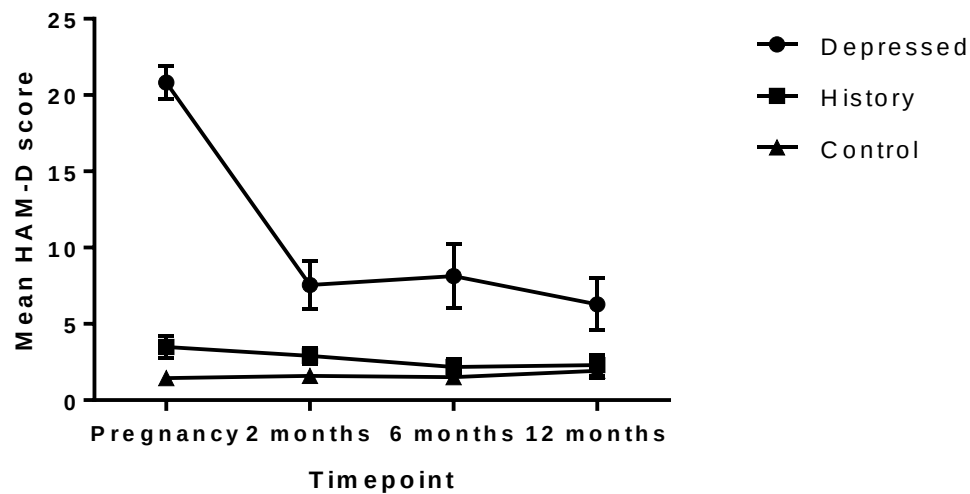


Figure 3.5: Trajectory of mean HAM-D scores for the depressed, history and control groups across the pregnancy, two, six and twelve month time-points. Significant group differences are indicated in Table 3.3 and Figure 3.2

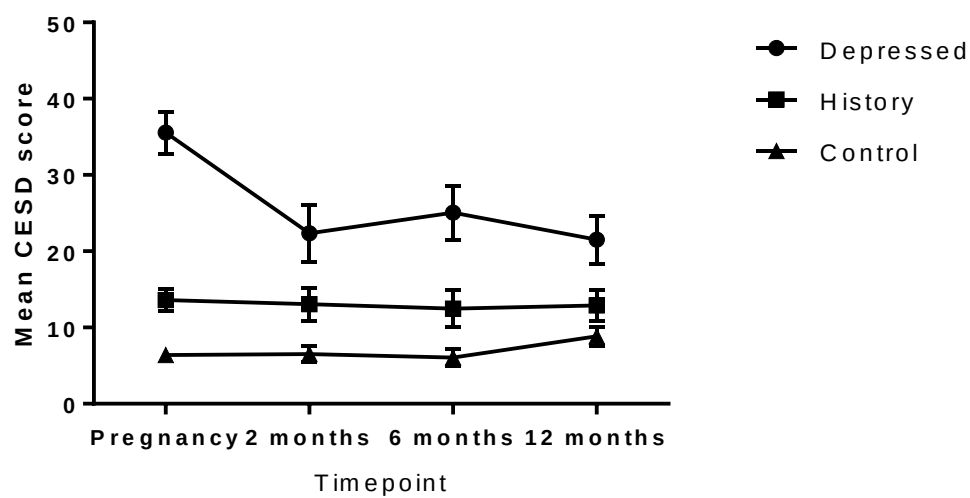


Figure 3.6: Trajectory of mean CESD scores for the depressed, history and control groups across the pregnancy, two, six and twelve month time-points. Significant group differences are indicated in Table 3.3 and Figure 3.5

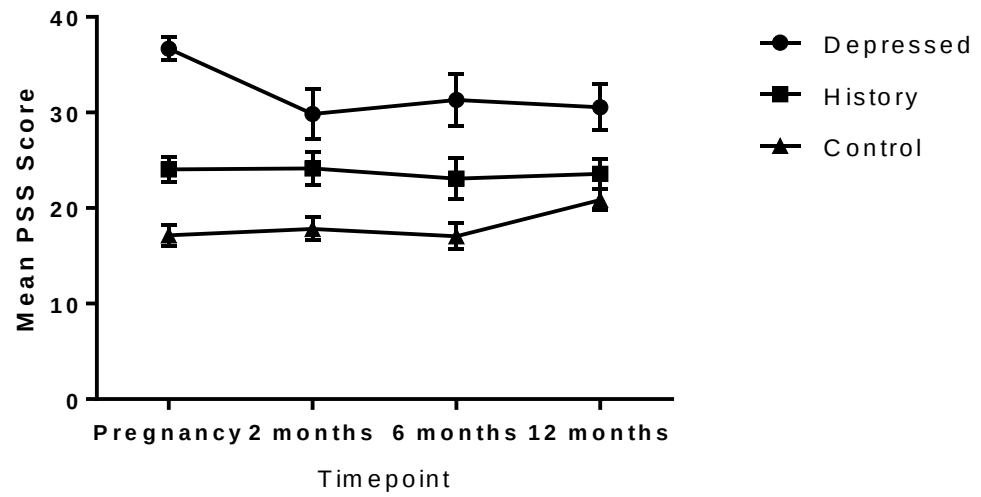


Figure 3.7: Trajectory of mean PSS scores for the depressed, history and control groups across the pregnancy, two, six and twelve month time-points. Significant group differences are indicated in Table 3.3 and Figure 3.4

3.3.5 Infant demographic and birth characteristics

Infant demographic and birth characteristics are summarised in Table 3.4. There were significant group differences for gestational age at birth [χ^2 (2, 99) =14.653, $p<.001$]. Both the Depressed group [$U=245$, $z=-3.361$, $p=.001$] and History group [$U=497.5$, $z=-2.398$, $p=.016$] had a significantly lower gestational age compared with the Control group. One infant in the Depressed group was born at 36 weeks and to avoid the potential confounding effects of a lower gestational age, the data for this infant was removed from the NBAS analysis but was retained for all other analyses. All remaining infants were born at term (Range: 37-42 weeks). At 12 months there were significant group differences for childcare [χ^2 (76) =7.522, $p=.023$]. Post-hoc analyses using the Mann-Whitney U test indicated that infants in the Control group were in childcare for a significantly longer duration per week compared with the Depressed group [$U=129$, $z=-2.774$, $p=.006$]. There were no significant differences in hours spent in childcare per week between groups at 6 months. There were no significant group differences for birthweight, infant sex, delivery method or breastfeeding. Lastly, there were no differences between the infants whose mothers took antidepressant medication during pregnancy and those that didn't in any of the infant neurodevelopment measures.

Table 3.4: Infant demographic and birth characteristics

Infant	Depressed (n=23)	History (n=34)	Control (n=43)
Gestational Age at birth (mean, SD)	39.09(1.4)***	39.6* (1.19)	40.42 (1.1)
Birthweight, kg (mean, SD)	3.46 (.48)	3.77 (.46)	3.7 (.49)
Sex (male, %)	12 (52.2%)	19 (55.9%)	30 (69.8%)
Delivery Method (n, %)			
Vaginal	19 (82.6%)	25 (73.5%)	33 (76.7%)
C-Section	2 (8.7%)	6 (17.6%)	7 (16.3%)
Elective C-Section	2 (8.7%)	3 (8.8%)	3 (7%)
Breastfed (n, %)	13 (76.5%)	23(85.2%)	30(84.6%)
Hours of childcare per week (mean, SD)			
6 months	4.82 (9.97)	2.59(7.29)	5.54 (12.43)
12 months	23.13 (14.35)**	11.1 (15.2)	22.39 (17.74)

*p<.05 **<.01

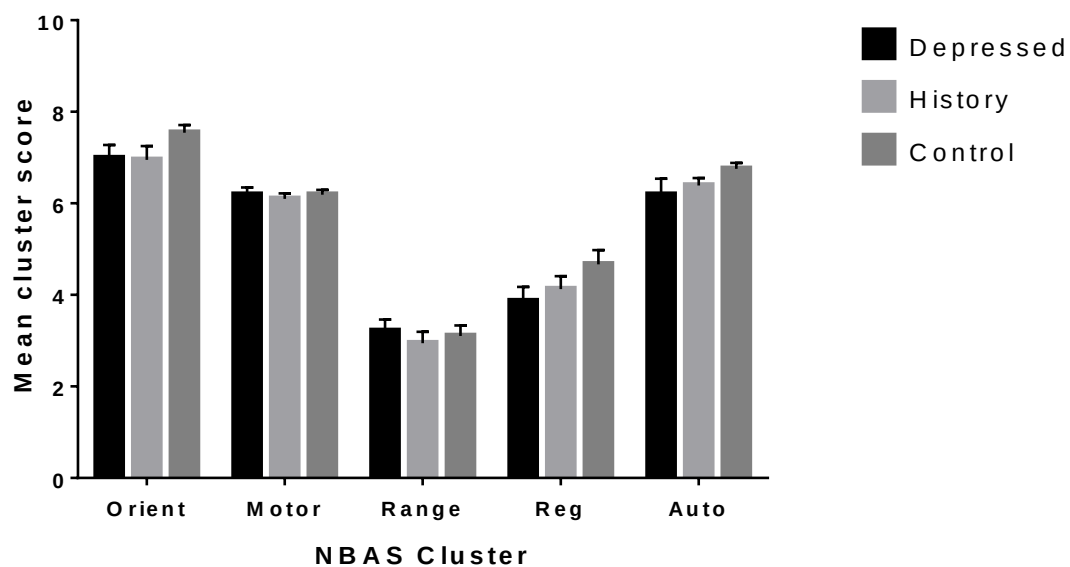
3.3.6 Neonatal Behavioural Assessment Scale (NBAS)

Group Comparisons

As the majority of infants were awake on arrival, the habituation cluster was omitted from the analysis due to the requirement of this item for the infant to be asleep. The Kruskal-Wallis Test was conducted to assess group differences. There were no significant differences between the groups on any of the NBAS clusters or supplementary items. Group means and chi-square statistics are presented in Table 3.5 and Table 3.6. Mean group scores are plotted in Figures 3.8 and 3.9.

Table 3.5: Mean scores and group comparisons for each of the five NBAS clusters.

	Depressed (n=13)	History (n=29)	Control (n=30)	
<i>NBAS Cluster</i>	<i>Mean (SD)</i>	<i>Mean (SD)</i>	<i>Mean (SD)</i>	<i>Statistic, p value</i>
Orientation	6.99 (.96)	6.95 (1.52)	7.54 (.85)	$\chi^2=2.443$, $p=0.295$
Motor	6.19 (.59)	6.1 (.61)	6.2 (.58)	$\chi^2=1.192$, $p=0.551$
Range of State	3.2 (.92)	2.94 (1.3)	3.1 (1.23)	$\chi^2=0.369$, $p=0.832$
Regulation of State	3.9 (1.16)	4.13 (1.47)	4.67 (1.67)	$\chi^2=2.074$, $p=0.355$
Autonomic Stability	6.19 (1.3)	6.39 (.86)	6.5 (.922)	$\chi^2=5.083$, $p=0.079$

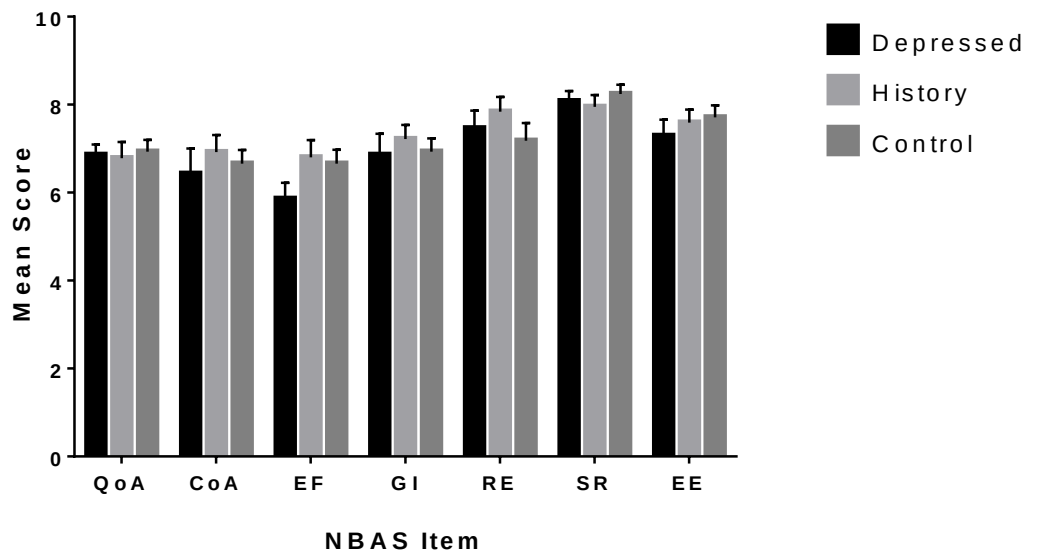


Orient: Orientation, Range: Range of State, Reg: Regulation of State, Auto: Autonomic

Figure 3.8: Group comparisons of mean scores for each of the five NBAS clusters.

Table 3.6: Mean scores and group comparisons for each of the seven supplementary items of the NBAS.

	Depressed (n=13)	History (n=27)	Control (n=29)	
<i>NBAS Item</i>	<i>Mean (SD)</i>	<i>Mean (SD)</i>	<i>Mean (SD)</i>	<i>Statistic, p value</i>
Quality of Alertness	6.86 (.864)	6.78 (1.93)	6.93 (1.44)	$\chi^2=0.088$, $p=0.957$
Cost of Attention	6.43 (2.14)	6.92 (1.98)	6.66 (1.65)	$\chi^2=0.696$, $p=0.706$
Examiner Facilitation	5.86 (1.35)	6.8 (1.98)	6.66 (1.7)	$\chi^2=3.724$, $p=0.155$
General Irritability	6.86 (1.79)	7.22 (1.65)	6.93 (1.59)	$\chi^2=0.522$, $p=0.770$
Robustness & Endurance	7.46 (1.45)	7.84 (1.68)	7.18 (2.11)	$\chi^2=2.824$, $p=0.244$
State Regulation	8.08 (.793)	7.95 (1.17)	8.24 (1.05)	$\chi^2=2.060$, $p=0.357$
Examiner's Emotional Response	7.29 (1.38)	7.59 (1.55)	7.71 (1.44)	$\chi^2=1.060$, $p=0.589$



QofA: Quality of Alertness, COA: Cost of Attention, EF: Examiner Facilitation, GI: General Irritability, RE: Robustness and Endurance, SR: State Regulation, EE: Examiners Emotional Response

Figure 3. 9: Mean scores for the NBAS supplementary items for the Depressed, History and Control groups at 2 months.

3.3.7 Bayley Scale of Infant Development (BSID)

Cognitive, Language and Motor Subscales

Group Comparisons

For group comparisons dummy-coded multivariate linear regression analyses were conducted for the Depressed and History groups with the Control group as the reference condition. To compare the Depressed and History group, a second analysis was conducted using the Depressed group as the reference condition. The mean and standard deviation for the BSID cognitive, language and motor scores for each group at six and twelve months are summarised in table 3.7.

Table 3.7: Mean scores for each subscale of the BSID at 6 and 12 months. Group comparisons are reported in the text.

	Depressed	History	Control
<i>6 months</i>	<i>Mean (SD)</i>	<i>Mean (SD)</i>	<i>Mean (SD)</i>
Cognitive	104.29 (10.99)	106.55 (8.25)	105.26 (6.25)
Language	93.8 (11.87)	93.61 (9.49)	97.08 (7.18)
Motor	95.48 (11.87)	96.49 (20.26)	99.97 (10.64)
<i>12 Months</i>			
Cognitive	111.32 (11.77)	107.41 (11.21)	106.84 (11.94)
Language	87.33 (10.54)	94.04 (9.42)	95.06 (11.78)
Motor	90.94 (11.52)	92.35 (10.08)	93.51 (9.05)

6 months

There were no significant differences between either the Depressed or History group compared with Controls for the cognitive [$F(2, 85) = .280, p = .757$], language [$F(2, 83) = .428, p = .653$] or motor [$F(2, 83) = .708, p = .495$] subscales of the BSID at 6 months. There were also no differences between the History or Depressed group for the same three subscales; cognitive [$F(2, 85) = .182, p = .834$], language [$F(2, 83) = 2.609, p = .080$], motor [$F(2, 83) = .138, p = .871$]. Regression coefficients for the above models are presented in Table 3.8. Mean scores for each group are presented in Figure 3.10

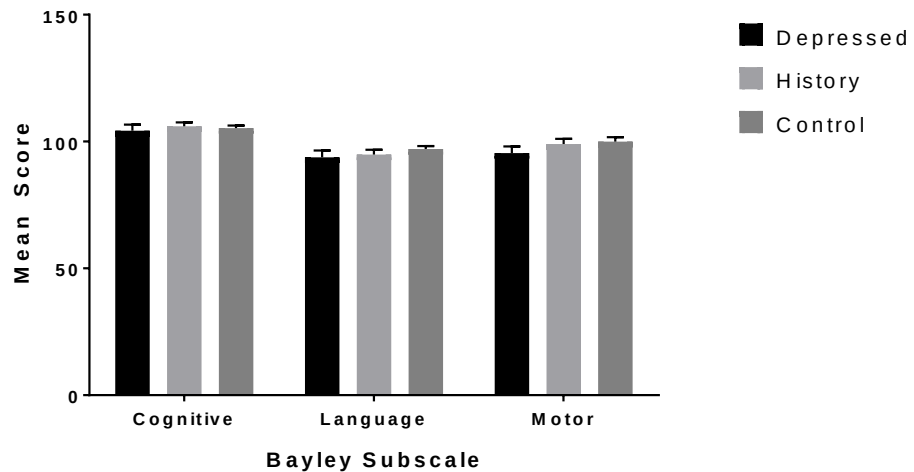


Figure 3. 20: Mean scores for the cognitive, language and motor scales of the Bayley Scale of Infant Development for the Depressed, History and Control groups at 6 months.

12 months

There were no significant differences between Depressed or History group compared with Controls for the cognitive [$F(2, 82) = .927, p = .4$] or the motor [$F(2, 79) = .426, p = .655$] subscales of the BSID. However, there were significant differences between the groups on the language subscale [$F(2, 74) = 3.287, p = .043$]. At 12 months, the Depressed group had lower scores on the language scale ($\beta = -.299, p = .015$) compared with Controls. This difference remained after adding covariates to the model ($\beta = -.293, p = .019$).

However, after adding maternal 12m CESD score the model was no longer significant ($\beta=-.231$, $p=.118$). Regression coefficients for the models are presented in Table 3.9. Mean scores for each group are presented in Figure 3.11.

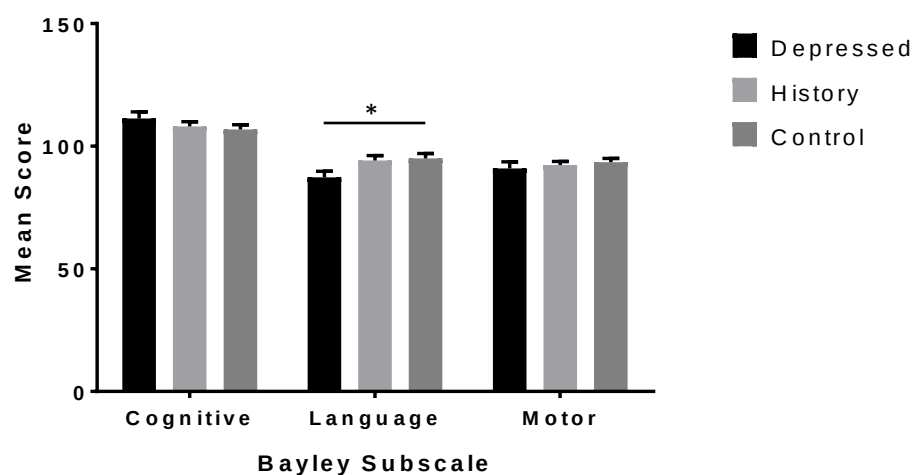


Figure 3. 11: Mean scores for the cognitive, language and motor scales of the Bayley Scale of Infant Development for the Depressed, History and Control groups at 12 months.

Table 3.8: Effects of group on the Cognitive, Language and Motor Subscales of the Bayley at 6 months.

		Cognitive						Language						Motor					
		B	SE	beta	t	p	Adj. R2	B	SE	beta	t	p	Adj. R2	B	SE	beta	t	p	Adj. R2
Model 1 ^a	Intercept	105.246	1.320		79.731	.000	-.017	96.652	1.525		63.371	.000	-.014	99.519	1.805		55.141	.000	-.007
	Depressed vs Control	-1.018	2.287	-.052	-.445	.657		-2.077	2.643	-.093	-.786	.434		-3.615	3.127	-.136	-1.156	.251	
	History vs Control	.772	2.000	.045	.386	.700		-1.737	2.311	-.089	-.752	.454		-.487	2.735	-.021	-.178	.859	
	Intercept	104.839	1.701		61.630	.000	-.019	92.662	1.914		48.408	.000	.036	97.513	2.339		41.688	.000	-.021
	Depressed vs History	1.172	2.204	.069	.532	.596		1.956	2.480	.100	.789	.433		1.447	3.031	.062	.477	.634	
Model 2 ^b	Intercept	100.464	4.496		22.345	.000	-.006	93.290	5.206		17.921	.000	-.007	90.378	6.199		14.579	.000	-.013
	Depressed vs Control	-1.149	2.289	-.059	-.502	.617		-1.750	2.650	-.078	-.660	.511		-3.300	3.156	-.124	-1.046	.299	
	History vs Control	.214	2.054	.013	.104	.917		-.633	2.378	-.032	-.266	.791		.043	2.832	.002	.015	.988	
	Intercept	99.954	4.454		22.440	.000	-.010	90.968	5.038		18.055	.000	.036	88.838	6.173		14.391	.000	-.027
	Depressed vs History	.655	2.231	.038	.294	.770		2.617	2.524	.134	1.037	.303		1.432	3.092	.062	.463	.644	
Model 3 ^c	Intercept	102.384	4.994		20.502	.000	.024	94.744	5.854		16.184	.000	-.011	89.476	7.093		12.614	.000	-.037
	Depressed vs Control	1.962	2.940	.100	.667	.507		.606	3.446	.027	.176	.861		-4.762	4.176	-.179	-1.140	.258	
	History vs control	1.542	2.335	.090	.660	.511		.373	2.737	.019	.136	.892		-.581	3.317	-.025	-.175	.861	
	Intercept	104.799	5.249		19.965	.000	.039	92.299	6.133		15.050	.000	.012	88.312	7.589		11.636	.000	.034
	Depressed vs History	-.918	2.504	-.054	-.367	.715		2.185	2.926	.112	.747	.458		1.603	3.621	.069	.443	.659	

^a group only; ^b group with parity, education and infant sex; ^c group with parity, education, infant sex and maternal 6 month Center for Epidemiological Studies Depression (CESD) score.

Table 3.9: Effects of group on the Cognitive, Language and Motor Subscales of the Bayley at 12 months.

		Cognitive						Language						Motor					
		B	SE	beta	t	p	Adj. R2	B	SE	beta	t	p	Adj. R2	B	SE	beta	t	p	Adj. R2
Model 1 ^a	Intercept	106.829	1.923		55.554	.000	-.002	95.046	1.850		51.379	.000	.057	93.541	1.649		56.719	.000	-.014
	Depressed vs Control	4.522	3.332	.160	1.357	.178		-7.948	3.206	-.299	-2.479	.015		-2.596	2.858	-.110	-.909	.366	
	History vs Control	1.212	2.914	.049	.416	.679		-.952	2.804	-.041	-.340	.735		-1.239	2.499	-.060	-.496	.621	
	Intercept	110.711	2.480		44.642	.000	-.005	88.216	2.398		36.795	.000	.044	91.283	2.124		42.967	.000	-.016
	Depressed vs History	-2.456	3.213	-.100	-.764	.447		5.500	3.107	.236	1.770	.081		.893	2.753	.043	.324	.747	
Model 2 ^b	Intercept	99.563	6.573		15.147	.000	.002	95.753	6.382		15.004	.000	.043	89.406	5.679		15.744	.000	-.026
	Depressed vs Control	4.273	3.346	.151	1.277	.205		-7.788	3.249	-.293	-2.397	.019		-2.484	2.891	-.105	-.859	.393	
	History vs Control	.795	3.003	.032	.265	.792		-.044	2.915	-.002	-.015	.988		-.405	2.594	-.020	-.156	.876	
	Intercept	102.615	6.507		15.771	.000	.002	90.329	6.358		14.207	.000	.029	87.740	5.626		15.595	.000	-.029
	Depressed vs History	-2.774	3.259	-.112	-.851	-.2774		6.227	3.185	.268	1.955	.054		1.488	2.818	.072	.528	.599	
Model 3 ^c	Intercept	98.718	7.067		13.968	.000	-.013	96.839	6.835		14.168	.000	.033	87.574	6.006		14.581	.000	-.003
	Depressed vs Control	2.990	4.007	.106	.746	.458		-6.138	3.875	-.231	-1.584	.118		-5.267	3.405	-.223	-1.547	.127	
	History vs Control	.305	3.258	.012	.094	.926		.585	3.151	.025	.186	.853		-1.467	2.769	-.071	-.530	.598	
	Intercept	100.768	7.314		13.777	.000	-.013	92.956	7.103		13.086	.000	.025	84.385	6.249		13.504	.000	-.014
	Depressed vs History	-2.198	3.533	-.089	-.622	.536		5.409	3.432	.232	1.576	.120		2.533	3.019	.123	.839	.404	

^a group only; ^b group with parity, education and infant sex; ^c group with parity, education, infant sex and maternal 12 month Center for Epidemiological Studies Depression (CESD) score.

Social-Emotional and Adaptive Behaviour

Group Comparisons

Dummy-coded multivariate linear regression analyses were conducted to compare the Depressed, History and Control groups on the Social-Emotional and Adaptive Behaviour scales of the BSID. The mean and standard deviation for the social-emotional and the adaptive behaviour scales of the BSID scores at two, six and twelve months are summarised in table 3.10.

Table 3.10: Mean scores for the SE and AB questionnaires for each group at the 2, 6 and 12 month time-points. Group comparisons are reported in the text.

	Depressed <i>Mean (SD)</i>	History <i>Mean (SD)</i>	Control <i>Mean (SD)</i>
<i>2 months</i>			
Social-Emotional	104.58 (18.76)	99.61 (13.69)	103.42 (11.77)
Adaptive Behaviour	103.08 (15.79)	94.49 (22.5)	106.94 (13.27)
<i>6 months</i>			
Social-Emotional	108.46 (15.46)	99 (16.2)	101.67 (15.8)
Adaptive Behaviour	103.64 (9.68)	102.04 (11.74)	106.91 (14.99)
<i>12 months</i>			
Social-Emotional	107 (18.88)	111.04 (20.9)	107.71 (14.52)
Adaptive Behaviour	98.53 (11.95)	96.11 (10.68)	97 (10.08)

Two months

At two months (Table 3.11) there were no significant differences on the Social Emotional Scale of the BSID between the Control group compared with the Depressed or History groups [$F(2, 70) = .653, p = .523$] or between the Depressed and History groups [$F(2, 70) = .634, p = .534$]. On the Adaptive Behaviour Scale there were significant group

differences in the model comparing the Control group with the Depressed and History groups [$F(2, 67) = 3.261, p = .045$]. At 2 months, the History group had significantly lower scores on the Adaptive Behaviour Scale compared with the Control group ($\beta = -.322, p = .013$). This effect remained after controlling for covariates ($\beta = -.349, p = .010$) and after controlling for maternal 2 month CES-D score ($\beta = -.312, p = .032$). There were no significant differences between the Depressed and Control group ($\beta = -.119, p = .350$) or between the History and the Depressed group [$F(2, 67) = 3.020, p = .056$].

Six months

At six months (Table 3.12) there were no significant differences on the Social Emotional Scale of the BSID between the Control group compared with the Depressed or History groups [$F(2, 68) = 1.765, p = .179$] or with the comparison between Depressed and History groups [$F(2, 68) = 2.303, p = .108$]. Furthermore there were no significant differences on the Adaptive Behaviour Scale of the BSID at six months between the Control group compared with the Depressed or History groups [$F(2, 70) = 1.010, p = .370$] or with the comparison between Depressed and History groups [$F(2, 70) = .987, p = .378$].

Twelve months

At twelve months (Table 3.13) there were no significant differences on the Social Emotional Scale of the BSID between the Control group compared with the Depressed or History groups [$F(2, 73) = .346, p = .709$] or with the comparison between Depressed and History groups [$F(2, 73) = .327, p = .722$]. Furthermore there were no significant differences on the Adaptive Behaviour Scale of the BSID at twelve months between the Control group compared with the Depressed or History groups [$F(2, 68) = .214, p = .808$] or with the comparison between Depressed and History groups [$F(2, 68) = .201, p = .818$].

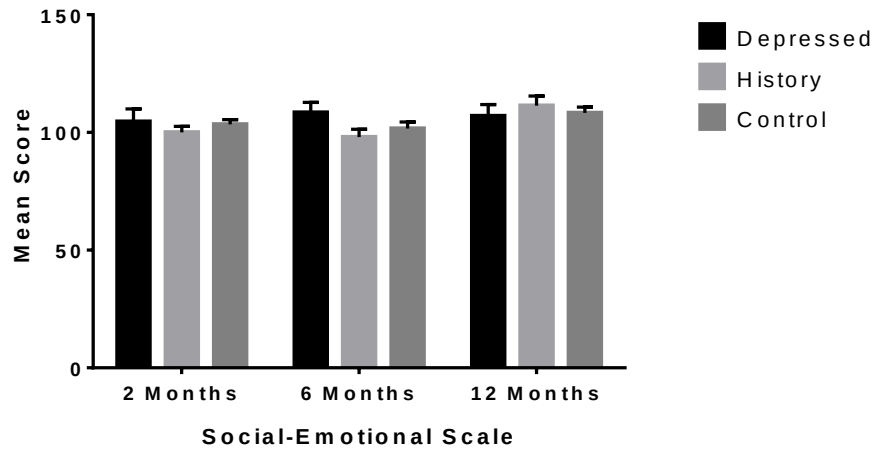


Figure 3.15: Mean Social-Emotional scores for the Depressed, History and Control groups at two, six and twelve months.

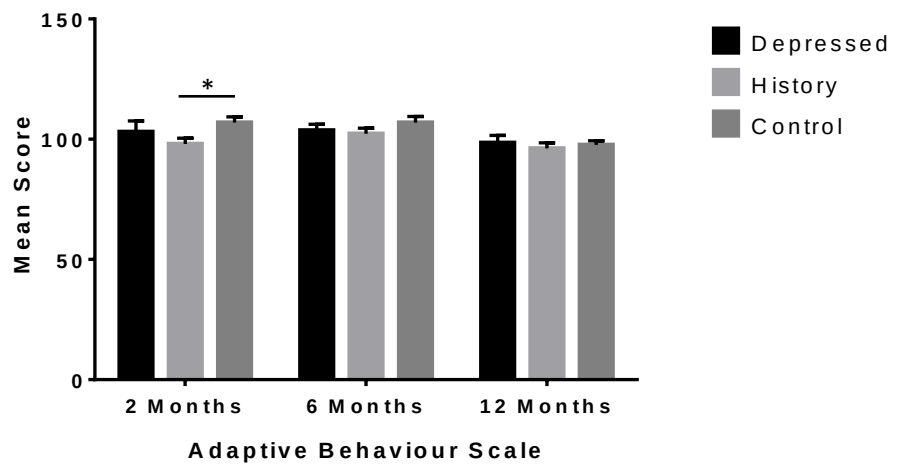


Figure 3.16: Mean Adaptive Behaviour scores for the Depressed, History and Control groups at two, six and twelve months.

Table 3.11: Effects of group on the Social-Emotional and Adaptive Behaviour Subscales of the Bayley at 2 months.

	2 months	Social-Emotional					Adaptive Behaviour						
		B	SE	beta	t	p	Adj. R2	B	SE	beta	t	p	Adj. R2
Model 1 ^a	Intercept	103.305	2.440		42.338	.000	-.010	107.014	2.422		44.179	.000	.062
	Depressed vs Control	.906	4.230	.027	.214	.831		-3.949	4.200	-.119	-.940	.350	
	History vs Control	-3.537	3.699	-.123	-.956	.342		-9.378	3.672	-.322	-2.554	.013	
	Intercept	103.393	3.142		32.903	.000	-.010	104.096	3.129		33.266	.000	.055
	Depressed vs History	-3.645	4.073	-.126	-.895	.374		-6.604	4.056	-.227	-1.628	.108	
Model 2 ^b	Intercept	99.588	8.343		11.937	.000	-.006	114.603	8.412		13.624	.000	.036
	Depressed vs Control	.839	4.247	.025	.198	.844		-4.179	4.283	-.126	-.976	.333	
	History vs Control	-4.879	3.811	-.169	-1.280	.205	-.007	-10.152	3.843	-.349	-2.642	.010	
	Intercept	99.812	8.254		12.092	.000		111.790	8.340		13.404	.000	.031
	Depressed vs History	-4.953	4.135	-.172	-1.198	.235		-6.950	4.178	-.239	-1.663	.101	
Model 3 ^c	Intercept	101.910	8.972		11.359	.000	-.014	116.874	9.061		12.899	.000	.027
	Depressed vs Control	3.218	5.164	.097	.623	.535		-1.852	5.215	-.056	-.355	.724	
	History vs Control	-3.789	4.109	-.131	-.922	.360		-9.086	4.150	-.312	-2.190	.032	
	Intercept	102.626	9.540		10.757	.000	-.019	115.989	9.613		12.066	.000	.026
	History vs Control	-5.493	4.331	-.190	-1.268	.209		-7.755	4.364	-.266	-1.777	.081	

^a group only; ^b group with parity, education and infant sex; ^c group with parity, education, infant sex and maternal 6 month Center for Epidemiological Studies Depression (CESD) score.

Table 3.12: Effects of group on the Social-Emotional and Adaptive Behaviour Subscales of the Bayley at 6 months.

	6 months	Social-Emotional					Adaptive Behaviour						
		B	SE	beta	t	p	Adj. R2	B	SE	beta	t	p	Adj. R2
Model 1 ^a	Intercept	101.465	2.872		35.329	.000	.021	107.058	2.306		46.421	.000	.000
	Depressed vs Control	6.222	4.979	.160	1.250	.216		-3.312	3.998	-.106	-.828	.410	
	History vs Control	-3.571	4.354	-.105	-.820	.415		-4.836	3.496	-.176	-1.383	.171	
	Intercept	108.124	3.670		29.459	.000	.036	104.114	2.970		35.053	.000	.000
	Depressed vs History	-9.816	4.757	-.288	-2.063	.043		-2.059	3.850	-.075	-.535	.595	
Model 2 ^b	Intercept	104.607	9.847		10.624	.000	.020	105.105	8.059		13.042	.000	-.041
	Depressed vs Control	5.333	5.013	.137	1.064	.291		-3.406	4.103	-.109	-.830	.409	
	History vs Control	-4.303	4.498	-.126	-.957	.342		-4.716	3.682	-.172	-1.281	.205	
	Intercept	108.899	9.690		11.238	.000	.030	102.686	7.976		12.875	.000	-.042
	Depressed vs History	-9.562	4.854	-.281	-1.970	.053		-1.896	3.995	-.069	-.474	.637	
Model 3 ^c	Intercept	107.954	10.372		10.408	.000	.042	105.652	8.598		12.288	.000	-.062
	Depressed vs Control	10.758	6.106	.276	1.762	.083		-2.519	5.062	-.080	-.498	.621	
	History vs Control	-1.987	4.850	-.058	-.410	.684		-4.337	4.021	-.158	-1.079	.285	
	Intercept	117.205	10.858		10.794	.000	.065	103.951	9.113		11.407	.000	-.062
	Depressed vs History	-12.259	5.180	-.360	-2.367	.021		-2.306	4.348	-.084	-.530	.598	

^a group only; ^b group with parity, education and infant sex; ^c group with parity, education, infant sex and maternal 6 month Center for Epidemiological Studies Depression (CESD) score.

Table 3.13: Effects of group on the Social-Emotional and Adaptive Behaviour Subscales of the Bayley at 12 months.

	12 months	Social-Emotional						Adaptive Behaviour					
		B	SE	beta	t	p	Adj. R2	B	SE	beta	t	p	Adj. R2
Model 1 ^a	Intercept	108.299	3.057		35.428	.000	-.018	97.679	1.940		50.343	.000	-.023
	Depressed vs Control	-1.164	5.298	-.028	-.220	.827		.828	3.364	.032	.246	.806	
	History vs Control	3.048	4.633	.083	.658	.513		-1.373	2.941	-.061	-.467	.642	
	Intercept	107.598	3.937		27.333	.000	-.018	98.318	2.499		39.349	.000	-.023
	Depressed vs History	3.720	5.102	.101	.729	.468		-1.979	3.239	-.088	-.611	.543	
Model 2 ^b	Intercept	97.095	10.375		9.358	.000	.000	107.354	6.587		16.299	.000	-.005
	Depressed vs Control	-1.549	5.282	-.037	-.293	.770		.147	3.353	.006	.044	.965	
	History vs Control	1.675	4.740	.046	.354	.725		-1.973	3.009	-.088	-.656	.514	
	Intercept	96.255	10.269		9.374	.000	-.001	107.197	6.513		16.458	.000	-.004
	Depressed vs History	2.525	5.144	.069	.491	.625		-1.659	3.263	-.074	-.508	.613	
Model 3 ^c	Intercept	97.538	10.765		9.060	.000	-.016	106.430	6.761		15.741	.000	-.012
	Depressed vs Control	-.876	6.103	-.021	-.144	.886		-1.256	3.833	-.049	-.328	.744	
	History vs Control	1.932	4.963	.053	.389	.698		-2.509	3.117	-.112	-.805	.424	
	Intercept	97.473	11.142		8.748	.000	-.016	105.105	6.985		15.046	.000	-.008
	Depressed vs History	2.146	5.383	.058	.399	.691		-1.007	3.375	-.045	-.298	.766	

^a group only; ^b group with parity, education and infant sex; ^c group with parity, education, infant sex and maternal 6 month Center for Epidemiological Studies Depression (CESD) score.

3.4 Discussion

3.4.1 Overview of Results

The aim of this study was to assess the impact of depression during pregnancy on infant neurodevelopmental outcome during the first postnatal year in a sample of mothers with a clinical diagnosis of Major Depressive Disorder, a History of Major Depressive Disorder and a Control group with no History of psychiatric disorder.

Maternal depression was measured during pregnancy and at the three postnatal time-points, two months, six months and twelve months, using the Hamilton Rating Scale for Depression (HAM-D) and the Center for Epidemiological Studies Depression Scale (CESD). Mothers in the Depressed Group had significantly higher HAM-D Scores and CESD scores compared with mothers in the History and Control groups at all four time-points. Mothers in the History Group had significantly higher HAM-D scores compared with Controls at pregnancy and two months postpartum and higher CESD scores during pregnancy, two and six months post-partum. There were no significant differences between the History and Control groups for HAM-D scores at six or twelve months or for CESD scores at twelve months.

At two months infant neurobehavioral development was measured using the Neonatal Behavioural Assessment Scale (NBAS) and within this study there were no group differences in any of the five clusters of the NBAS or for any of the supplementary items. There were also no group differences on the Social-Emotional Scale at this time-point. However for the Adaptive Behaviour Scale, infants in the History group had significantly lower scores than the Depressed and Control group. At six months and twelve months, infant neurodevelopment was assessed using the BSID Scale of Infant Development (BSID). At the six month time-point there were no significant differences between the three groups on the cognitive, language and motor scales of the BSID Scale of Infant Development. At twelve months there were no differences between the three groups on the cognitive and motor scales. However at this time-point, the Depressed

group had significantly lower language scores compared to the Control group. This association held after adjusting for covariates but attenuated after controlling for self-rated maternal depressive symptoms at that time-point. There were no group differences for the Social-Emotional Scale or the Adaptive Behaviour Scale at six or twelve months.

3.4.2 Trajectories of Depression across the perinatal period.

One of the most important aspects to note about this data are the trajectories of depression scores across the perinatal period for each of the three groups. The trajectories of depression scores for the History and Control groups across the four points of the study remain consistent over time. However, for the Depressed group there is a marked reduction in mean depression scores, measured by the both the HAM-D and the CES-D from pregnancy to two months, increasing slightly at 6 months, and decreasing again at the twelve month time-point. The lack of group differences in this study, may be reflective of the reduction in depression scores reported by the mothers in the postnatal period. There is much debate around which aspects of maternal depression, be it the timing, severity or chronicity of symptoms, play the most important role in predicting offspring outcome. As this aspect of the data is integral to each element of this study, it will be discussed in more detail in the general discussion.

3.4.3 Infant Neurobehavioral Development at two months: Neonatal Behavioural Assessment Scale

At two months there were no group differences in any of the five clusters of the NBAS. Thus, the data in this study did not support the hypothesis that the Depressed group would have lower NBAS scores compared with Controls. There were also no significant group differences in any of the supplementary items of the NBAS. These results are contrary to what has previously been reported in infants born to mothers with antenatal

depressive symptoms using the NBAS. Among these studies it has been reported that infants of mothers with antenatal depressive symptoms have lower scores on clusters of the NBAS such as orientation, motor and state regulation scales (Field et al., 2001; Goodman et al., 2011; Hernandez-Reif et al., 2006). The supplementary items are not commonly reported within the literature and therefore it cannot be said whether the data in the current study is supportive of the previous research. However, infants in the Depressed group did not demonstrate increased fussing or crying behaviours previously reported by Diego et al (2005). These aspects of behaviour are captured within the *General Irritability* and *State Regulation* items of the supplementary scales and did not demonstrate group differences within this study.

This data also did not support the hypothesis that there would be significant differences between the infants in the History group compared with the Depressed or Control group. In line with this finding, Suri et al (2011) also reported no differences between the NBAS scores in infants of women with a history of depression compared with controls. It may be the case that infants born to women with a history of depression do have similar NBAS scores to infants born to control mothers. However as there were no differences between either the History or Control groups in comparison with the Depressed group, contrary to what has previously been reported, there may be an alternative reason for the NBAS outcomes in this study.

One notable difference between this study and those previously reported is the age at which the infants in this study were assessed. Within all of the previous studies using the NBAS to assess the possible impact of antenatal depression, infants were assessed in the timeframe of 24 hours to 1 week post birth. In our sample, infants were assessed at an average of 8 weeks with a range of 7 weeks to 10 weeks. Although the NBAS manual states that the assessment is suitable for infants up to 2 months of age, it is typically not used in the literature in infants older than one month. The only study in which the NBAS was used in infants older than one month was the above mentioned study by Suri et al (2011) who assessed their infants at 1 week and again at 6-8 weeks.

The NBAS does not provide standardised normative data thus it is difficult to compare infants of different ages, even infants that differ by just one week. Within this study, to try to keep the age at which the infant was assessed as consistent as possible, the NBAS was scheduled for when the infant was 8 weeks old. However, this was not always possible due to scheduling difficulties such as infant illness and as a result, some of the infants were assessed later than others.

Assessing infants as soon as possible following birth provides a unique opportunity to gather neurobehavioral data with minimal impact of the postnatal environment. As the infants in this study were considerably older than most of the infants in the previously reported studies in this area it is possible that aspects of the postnatal environment may have played a role reducing any differences between the three groups. In addition to maternal postnatal depressive symptoms, factors like supportive maternal caregiving can play an important role in infant development outcomes and it would be important to consider how this is impacted by depression during the perinatal period.

Finally, within this study NBAS data were only available for a subset of the infants in this sample. Due to this, the results must be interpreted with caution as inadequate power may have contributed to the finding that there were no significant differences between the three groups.

3.4.4 Bayley scale of Infant development at 6 and 12 months

At six months there were no significant differences between the three groups on the cognitive, language and motor scales of the BSID. At twelve months there were no differences between the three groups on the cognitive and motor scales of the BSID. However at twelve months, the Depressed group had significantly lower language scores in comparison to the Control group. This association held after adjusting for covariates

but was no longer significant after controlling for maternal depressive symptoms at that time-point.

There is very little research investigating the impact of antenatal depression on neurodevelopment in infants of twelve months and younger. Bhang and colleagues (2016) reported lower cognitive development scores in infants of six months born to mothers with higher depressive symptoms during their pregnancy. In our study, we found no effect of depression on cognitive or motor development. These results at least in part support the previous research that there is no impact of maternal depression during pregnancy on infant or child outcomes (Koutra et al., 2013; Tse et al., 2010; Hay et al., 2008; Maselko et al., 2015). This study is the first to assess the impact of antenatal depression on language development in infants of six and twelve months of age, thus there are no studies with infants of this age with which to compare our findings. However, the effect of depression during pregnancy on language development has been reported in older children. Brown et al (2016) reported an increased risk for the development of language disorder in a large cohort of mothers with antenatal depression ranging from birth to fourteen years. Additionally, Skurtveit et al (2014) reported lower language scores in the offspring of antenatally depressed mothers at age three, independent of postnatal depression.

The results of our data indicate that the impact of antenatal depression on language development may be seen in infants as young as twelve months of age. The difference between the groups attenuated when postnatal depressive symptoms were controlled for emphasising the contribution of current depression symptoms on infant development. Antenatal depression is a highly predictive factor for postnatal depression and may impact child language development indirectly in this manner. The relationship between postnatal depression and impaired language development has previously been reported within the literature (Quevedo et al., 2012). However, it is proposed that postnatal depression has an indirect effect on language development through the impact on the mother's behaviour. Mothers with postnatal depression express more

negative affect, focus less on infant experience within interactions and show less acknowledgement of infant agency (Murray, Kempton, Woolgar & Hooper, 1993). Mothers with postnatal depression also demonstrate impaired caregiving ability and read to their children less than non-depressed mothers both of which have a negative impact on child development (Paulson, Keefe & Leiferman, 2009; Stein, Malmberg, Sylva, Barnes, Leach et al., 2008). This indirect relationship is one that is also investigated as part of this thesis and will be reported and discussed further in a later chapter.

3.4.5 Social-Emotional and Adaptive Behaviour Scales

At two months infants in the History group had significantly lower scores than the Depressed and Control group on the Adaptive Scale of the BSID. However there were no significant group differences for both the Social-Emotional Scale at two, six or twelve months and the Adaptive Behaviour Scale at six and twelve months. As there were no differences between the Depressed and Control groups for the social-emotional and adaptive behaviour scales the data does not support the study hypothesis that infants in the Depressed group would have lower scores on these measures. This is surprising as impairments in social-emotional functioning are one of the more commonly reported findings within the antenatal depression literature (e.g. Eichler et al., 2017). However, these results are also in keeping with the rest of the study data which found, for the most part, no significant differences between the infants of the Depressed and Control groups.

Within this study, infants in the History group had lower adaptive behaviour scores at two months and this relationship remained after controlling for confounding variables and maternal depressive symptoms. This difference did not persist at the six and twelve month time-points. The adaptive behaviour score is a composite measure compiled from seven different scales which assesses the ability of the infant to accomplish functional tasks in different areas such as communication, leisure and self-

care. Husain et al (2012) have also reported lower adaptive behaviour scores in infants of depressed mothers at six months. The difference in adaptive behaviour scores at two months in this study may reflect group differences between infants in the History and Control group. However, these results must also be interpreted with caution due to the potential bias that is associated with current maternal depressive symptoms and the propensity to overstate children's behavioural problems (Chilcoat & Breslau, 1997; Najman et al., 2001).

3.4.6 Conclusions

At two months there were no differences between infants in the Depressed, History or Control group for any of the five clusters of the NBAS or for any of the supplementary items. This data is not in line with previous studies investigating the impact of antenatal depression in neonates, possibly due to differences in the ages at which the infants were assessed in this study and potential influences within the postnatal environment. There were no group differences at six and twelve months in the cognitive or motor scales of the BSID and therefore this data did not support the hypotheses of the study. Although there were no group differences in language development at six months, at twelve months the Depressed group had significantly lower language scores compared with the Control group. However, this relationship was no longer significant after controlling for maternal postnatal depressive symptoms. Antenatal depression is strongly associated with postnatal depression and thus may impact child language development indirectly in this manner. Additionally, there were no group differences for the Social-Emotional Scale at two, six or twelve months or the Adaptive Behaviour Scale at six and twelve months. At two months infants in the History group had significantly lower scores on the Adaptive Behaviour Scale compared with the Depressed and Control groups. Finally, consideration of the trajectory of maternal depression from the antenatal into the postnatal period may provide an explanation for the lack of observed differences between the three groups within this sample.

Chapter 4

Maternal hypothalamic pituitary adrenal axis
activity during pregnancy and infant
neurodevelopment

4.1. Overview

The Developmental Origins of Health and Disease (DOHaD) hypothesis proposes that early life experiences, particularly within the intrauterine environment, play a role in an individual's health outcomes later in life (O'Donnell & Meaney, 2017). This theory has recently been applied to explain the fetal origins of mental health, proposing that the mother's emotional well-being during pregnancy may have a significant impact on the neurodevelopment, endocrine, behavioural and emotional issues for the developing child (O'Donnell, Glover, Barker & O'Connor, 2014). However, the mechanisms that underlie the association between maternal mood during pregnancy and infant outcomes are not yet fully understood. Cortisol, a steroid hormone produced by the Hypothalamic-Pituitary-Adrenal (HPA) Axis is one of the proposed factors linking antenatal maternal mood and later offspring outcome as part of 'fetal programming'. This is due to the changes that occur within the maternal HPA axis during pregnancy, the key role that cortisol plays in certain aspects of fetal development, the role of cortisol in the endocrine response to stress and the relationship between increased cortisol and Major Depressive Disorder (MDD).

4.1.1 The Hypothalamic-Pituitary-Adrenal axis

The HPA axis comprises the body's stress responsive system which is responsible for the release of the glucocorticoid, cortisol (Giesbrecht, Campbell, Letourneau, Kooistra, Kaplan et al., 2012). Cortisol, together with corticotrophin releasing hormone (CRH) from the hypothalamus and adrenocorticotrophic hormone (ACTH) from the pituitary gland, play an important role in facilitating adaptation to stressful situations and restoration of homeostasis in humans (Miller and O'Callaghan, 2002). When faced with a stressor, a cascade of events commences within the HPA axis when CRH and arginine vasopressin (AVP) are released from the paraventricular nucleus of the hypothalamus which signals the release of ACTH from the anterior pituitary gland which then

stimulates the release of cortisol from the adrenal cortex. Additionally, the HPA axis also has a negative feedback loop whereby cortisol binds to receptors in the pituitary gland and hypothalamus essentially signalling a halt to the further release of cortisol. This prevents chronic exposure to cortisol within the brain which can have damaging effects on structure and function, particularly within the limbic system (Waffarn & Davis, 2012). In addition to the stress response system, cortisol is excreted in a distinct pattern over the course of a typical day. This diurnal rhythm is characterized by a peak in cortisol approximately 30 minutes after waking, known as the cortisol awakening response (CAR) and a subsequent decline of cortisol levels throughout the day (Edwards, Clow, Evans & Hucklebridge, 2001).

4.1.2 The maternal HPA axis in pregnancy

During pregnancy, basal cortisol levels increase steadily (Allolio, Hoffman, Linton, Winkelmann, Kusche et al. 1990), with an accelerated increase at approximately 25 weeks gestation. This is due to dramatic changes in regulation of the HPA axis as corticotrophin releasing hormone (CRH) is released from the placenta. Rather than a negative feedback loop, which outside of pregnancy would signal a halt on hypothalamic CRH production, placental CRH establishes a positive feedback loop. Over the course of gestation, this ensures the simultaneous increase of CRH, adrenocorticotrophic hormone (ACTH) and cortisol within the maternal and fetal compartments (King, Smith & Nicholson, 2001). Simultaneously, the placental enzyme 11 β -hydroxysteroid dehydrogenase type 2 (11 β HSD-2) protects the fetus from exposure to the increasing levels of maternal cortisol by converting it to its inactive form, cortisone (Cottrell & Seckl, 2009). Cortisol plays a critical role in fetal brain development and has a direct influence on neurogenesis, synaptogenesis and myelination as part of normal fetal brain maturation. The complex interplay of increasing cortisol and 11 β HSD-2 across pregnancy ensures that the fetus is exposed to adequate levels of cortisol across gestation.

4.1.3 Antenatal depression and the HPA axis

Major Depressive Disorder (MDD) is associated with abnormal patterns of cortisol secretion and hyperactivity of the HPA axis, likely due to hypersecretion of CRH from the hypothalamus, and impaired negative feedback within the HPA axis system (Pruessner, Hellhammer, Pruessner & Lupien, 2003). Despite the alterations to the HPA axis and the production of cortisol during pregnancy, chronic HPA axis hyperactivity has also been observed in pregnant women with depression, with evidence of higher evening cortisol levels (O'Keane, Lightman, Marsh, Pawlby, Papadopoulos et al., 2011; Peer, Soares, Levitan, Streiner & Steiner, 2013) and higher on average daily cortisol levels (O'Connor, Tang, Gilchrist, Moynihan, Pressman et al., 2014) compared with their non-depressed counterparts. Furthermore, newborns of antenatally depressed mothers have higher urinary cortisol levels and a blunted cortisol response to stress (Field, Diego, Dieter, Hernandez-Reif, Schanberg et al., 2004; Keenan, Gunthorpe & Grace, 2007). Higher basal cortisol levels and increased cortisol reactivity have also been observed in infants at six months and there is also evidence that overactive HPA axis activity persists through to early childhood (Brennan, Pargas, Walker, Green, Newport & Stowe, 2008; Gutteling, de Weerth & Buitelaar, 2005).

4.1.4 Impact of exposure to higher levels of cortisol on infant development

According to the fetal programming hypothesis, biological systems undergoing rapid development are particularly vulnerable to 'programming' influences (Gluckman & Hanson, 2004). The brain structures which make up the limbic system, such as the hypothalamus, hippocampus, amygdala and parts of the cerebral cortex, are particularly sensitive to exposure to cortisol during development due to the high expression of glucocorticoid receptors located within these regions (Weinstock, 1997). Previous research investigating the programming hypothesis have primarily focused on the hippocampus due to its key role in learning and memory (Squire & Wixted, 2011). Animal models have indicated a link between antenatal stress and increased exposure to

glucocorticoids *in utero* with disrupted hippocampal neurogenesis and reduced hippocampal volume (Dranovsky & Hen, 2006). Altered hippocampal structure has been demonstrated in adults exposed to psychological and psychosocial stress and in those with Major Depressive Disorder (Buss et al., 2012; Mareckova et al., 2018). In addition to the above, elevated late morning cortisol has also been associated with lower cognitive function in adulthood (Geoffroy, Hertzman, Li & Power, 2013).

Despite the associations between antenatal depression and increased maternal cortisol levels, few studies have looked at the potential adversarial impact of exposure to increased levels of cortisol *in utero* on infant outcomes or later childhood neurodevelopment. In younger infants higher antenatal maternal cortisol has been associated with negative emotionality (Davis et al., 2007; Baibazarova et al., 2013; Braithwaite et al., 2017), increased crying, fussing behaviours and negative facial expressions (De Weerth et al., 2003). In older infants, the reported relationship between maternal cortisol and neurodevelopment is less consistent with some studies reporting a negative impact on cognitive, language and motor development (Bergman et al., 2010; LeWinn et al., 2009; Buitelaar et al., 2003), while others have reported a positive impact (Davis & Sandman, 2010; Davis et al., 2017) or no relationship at all (Gutteling et al., 2005; Gutteling et al., 2006).

4.1.5 Methodological issues within the literature

Within the literature examining the relationship between antenatal cortisol and infant neurodevelopmental outcome there is huge variation in the measurement of cortisol, perhaps contributing to the variation in reported outcomes. These methodological issues predominantly lie in both 'how' and 'when' maternal cortisol is measured during the pregnancy. Within the literature, maternal cortisol is measured in saliva, amniotic fluid (e.g. Baibazarova et al., 2013; Bergman et al., 2010) and in plasma. Neither amniocentesis nor that of blood sample collection, allows for easy repeat sampling and

researchers are limited in terms of the time of day in which they can collect the sample. In addition, blood cortisol measurements include cortisol that is both bound and unbound to cortisol-binding globulin (CBG), the major transport protein for glucocorticoids (Sivukhina & Jirikowski, 2014). Only cortisol that is unbound is physiologically active (Matsui et al., 1979). CBG increases alongside oestrogen during pregnancy therefore, total cortisol evaluation is not a reliable indicator of physiologically active cortisol during pregnancy (Nenke et al., 2017). A solution to this problem is the measurement of salivary cortisol, all of which is unbound and physiologically active. Multiple cortisol samples are necessary to determine important aspects of the nature of cortisol secretion such as the diurnal slope. Moreover women undergoing amniocentesis tend to fall into an older age-bracket and also experience stress related to the procedure itself due to the increased risk of miscarriage and worry related to the outcome of the test results (Akolekar et al., 2015; Tercyak et al., 2001). Thus measuring cortisol in this way may introduce additional variance contributing to inaccuracies in reported results. As a result, salivary cortisol is often the most convenient and non-invasive way to collect samples for cortisol analysis.

The timeframe within which cortisol is sampled is also of particular importance in antenatal research due to both the diurnal nature of cortisol across the day and the nature of the maternal HPA axis during pregnancy. Due to the increasing levels of cortisol across pregnancy and the exponential increase which occurs approaching term, it is necessary that gestational age at the time of cortisol sampling is consistent across studies (O'Keane et al., 2011). Previous studies investigating the impact of antenatal cortisol on infant neurodevelopmental outcome have reported gestation ranges at recruitment 15 weeks (Davis et al., 2007) to 38 weeks (De Weerth et al., 2003). Across these studies, cortisol has also been sampled at various times between waking (De Weerth & Buitelaar, 2005) and late afternoon (Davis et al., 2007) and ranges from one sample on one day (LeWinn et al., 2009) to multiple times across one day (Buitelaar et al., 2003) or numerous times across pregnancy (Davis & Sandman, 2010). Ideally,

samples should be collected at multiple time-points across one day also capturing a stress response such as the cortisol awakening response within participants.

4.1.6 Study Outline

This study aimed to assess the relationship between antenatal maternal cortisol and infant neurodevelopmental outcome at two, six and twelve months. Participants collected five saliva samples over the course of one day to reflect the diurnal nature of cortisol secretion at one point during pregnancy. At two months infant neurobehavioral development was measured using the Brazelton Neonatal Behavioural Assessment Scale (NBAS) and at six and twelve months the BSID Scale of Infant Development (BSID) was used to assess infant cognitive, language and motor development. At all three time-points mothers also completed the social-emotional and adaptive behaviour questionnaires of the BSID.

Comparisons for maternal antenatal cortisol between the Depressed, History and Control groups recruited to this study have previously been reported in an unpublished thesis (Jairaj, 2017). No significant differences between the depressed, history and control groups for any of the cortisol indices during pregnancy were reported. Neither were there significant relationships between the measures of maternal mood and any of the maternal cortisol indices during pregnancy. As a result, this thesis considers whole sample associations between the maternal cortisol indices during pregnancy and the measures of infant neurodevelopmental outcome.

Hypotheses

- 1) Higher antenatal maternal cortisol would be negatively associated with infant scores on the NBAS at two months.

- 2) Higher antenatal maternal cortisol would be negatively associated with cognitive, language and motor scores at six and twelve months.
- 3) Higher antenatal maternal cortisol would be negatively associated with social-emotional development and adaptive behaviour at two, six and twelve months.

4.2 Method

4.2.1 Participants

Participants were recruited from the Perinatal Psychiatry services and antenatal booking clinics within the NMH, the CWIUH and the Rotunda Hospital in Dublin. Participants in their second or third trimester who met the inclusion and exclusion criteria were clinically assessed by Dr. Chaitra Jairaj, a research registrar in Psychiatry. Participants were recruited into a depressed, history or control group. Demographic data are presented in Chapter 3. For the purposes of this study analyses were run on the whole sample which included 98 mothers and their infants.

4.2.2 Measures

Maternal Demographic Characteristics

Maternal demographic information was recorded at the time of recruitment interview and included the following variables: maternal age, ethnicity, education, employment status and marital status.

Maternal health behaviours and obstetric factors

Maternal medication and current levels of cigarette and alcohol consumption were recorded. Details pertaining to the mother's obstetric history and current pregnancy were also recorded. These variables included: gravidity, parity, and any previous obstetric complications.

Maternal Clinical Measures

The MINI International Neuropsychiatric Interview (M.I.N.I.) (Sheehan et al., 1998) and the Hamilton Rating Scale for Depression (HAM-D) (Hamilton, 1960) were completed by Dr. Chaitra Jairaj at recruitment. Mothers also completed the Center for Epidemiologic Studies: Depression Scale (CES-D) (Radloff, 1977) and Perceived Stress Scale (PSS)

(Cohen, Kamarck & Mermelstein, 1983) on recruitment to the study and at 2, 6 and 12 months postpartum.

Infant Birth Characteristics

Infant birth details were obtained from participant medical records at each maternity hospital. In cases where these data were not available, the information was collected from the mother. Information on the mode of onset of labour, delivery method, infant gestational age at birth, weight at birth, 1 minute and 5 minute APGAR scores and head circumference were collected. Additional information on infant characteristics such as current weight, feeding method and hours of childcare per week were provided by the mother at the 2, 6 and 12 month time points.

Brazelton Neonatal Behavioural Assessment Scale-4th edition (NBAS) (Brazelton & Nugent, 2011).

The NBAS was carried out in a quiet, semi darkened room, with a temperature of 22-27°C in either the mother's house or in a room with the same conditions within TCIN where possible when the infant 8 weeks old. Mean infant age at assessment was 8 weeks, 1 day (Range: 7 weeks to 10 weeks 4 days). For analysis, data were grouped using the cluster-scoring method outlined by Lester, Als and Brazelton (1982) into seven domains: Habituation, Orientation, Motor, Range of State, Regulation of State, Autonomic Stability and Reflexes. In addition to these clusters, there are seven supplementary items which describes the infants overall performance over the course of the examination: Quality of Alertness, Cost of Attention, Examiner Facilitation, General Irritability, Robustness and Endurance, State Regulation, Examiner's Emotional Response. NBAS data are available for 72 of the infants within this study.

Bayley Scales of Infant Development-3rd Edition (BSID-III) (Bayley, 2006)

Infants were assessed using the BSID-III at 6 and 12 months of age. The BSID consists of five administered subtests: cognitive, receptive language, expressive language, fine motor and gross motor. Raw scores are converted to scaled scores, which account for age, using the appropriate table in the manual of the BSID-III. Three composite scores; Cognitive, Language and Motor, are obtained from the scaled score of the cognitive subtest, the sum of the scaled scores for both the receptive and expressive language subtests and the fine and gross motor scaled scores. At the 6 month time point, the mean age at testing was 6 months 13 days (Range: 5m 29 days to 7m 17 days). At the twelve month time point the mean age at testing was 12 months 19 days (Range: 12m 0 days to 14m 2 days).

Bayley-III Social-Emotional Scale (Greenspan, 2004)

The BSID Social-Emotional (SE) was completed by the mother at the 2, 6 and 12 month time points. All items are tallied and this comprises the SE raw score. This score is then converted to a scaled score and then to a composite score. The composite score for this measure is used for the purposes of the analysis.

Bayley-III Adaptive Behaviour Scales (Harrison & Oakland, 2003)

The Adaptive Behaviour Scales were completed by the mother at the 2, 6 and 12 month time points. The total score for each scale is tallied and converted to a General Adaptive Composite. The composite score for this measure is used for the purposes of the analysis.

4.2.3 Biological Measures

Maternal Salivary Cortisol

Participants collected saliva samples at one point during their pregnancy using Salivette™ swabs (Sarstedt). Mothers were asked to collect their saliva samples at five points across one day at the following times: Upon waking (0 minutes) and then 30 minutes, 60 minutes, 12 hours (720 minutes) and 12.5 hours (750 minutes) after waking. Mothers returned the saliva samples to Trinity College by post. Mean gestational age at which cortisol was sampled was 26.4 (+/- 3.85) weeks, range 18-34 weeks.

On return to Trinity College, Salivettes were centrifuged at 3500 rpm at 20°C for 15 minutes. Samples of 500µL of saliva were aliquoted into microtubes and stored at -80°C in Trinity College Institute of Neuroscience. Saliva samples were sent on dry ice using FEDEX courier services for analysis using liquid chromatography mass spectrometry (LC-MS) to Professor Brian Keevil's laboratory at the University Hospital of South Manchester.

The lower limit of detection for cortisol using LC-MS is <0.8 nm/l meaning that concentrations under this value cannot be detected. To minimise error in estimating the true values of cortisol within these samples, values of 0.8 were replaced with the value of the lower limit of detection divided by the square root of 2. This value is 0.57 (0.8/1.41) (Croghan, 2003). Before commencing analysis the cortisol data were screened for outliers and values of more than 3 standard deviations around the mean were removed from the dataset. This resulted in the removal of seven values in total, each from a different participant across the three groups: Depressed (n=2), History (n=4) and the control (n=1). Of these values, three were baseline (T0) values and the remaining four consisted of one from each additional timepoint (T30, T60, T720 & T750).

The cortisol indices used for the study included:

- (iv) *AUC with respect to ground (AUCg)*: is a variable that captures the total area under the curve where ground is equal to zero and is a measurement of total cortisol output.
- (v) *AUC with respect to increase (AUCi)*: AUCi is a variable that captures the AUC with respect to increase from baseline and emphasises the change of cortisol over time.
- (vi) *Slope*: the slope of the regression line fitted through the morning time points
- (vii) *PM average*: The average of the two evening cortisol values.
- (viii) *Diurnal Slope*: The slope of the regression line through the five time-points measured from waking to 12.5 hours post-waking.

Both raw cortisol values and log-transformed cortisol values were used to calculate the above parameters resulting in two sets of values. The Area Under the Curve (AUC) with respect to ground (AUCg) and the AUC with respect to increase (AUCi) were computed using formulae outlined by Fekedulegn and colleagues (2007).

4.2.4 Statistical Analyses

Data were assessed for normality using the Shapiro-Wilks test. Raw cortisol data were not normally distributed and were therefore log transformed in order to allow for analysis using general linear models. Following transformation, data that were normally distributed were analysed using Pearson's *r* correlations. Non-parametric correlation analyses were carried out using Spearman's *rho*. Raw cortisol values were used in analyses conducted with Spearman's *rho* correlations. Log-transformed cortisol values were used in analyses conducted using Pearson's correlations. All correlational analyses

were corrected for multiple comparisons using the False Discovery Rate (FDR) Method (Benjamini & Hochberg, 1995). All data were analysed using SPSS (Version 24, IBM).

4.3 Results

4.3.1 Maternal antenatal cortisol and NBAS clusters

Spearman's rho correlations were conducted to assess the relationship between maternal cortisol during pregnancy and the five clusters of the NBAS (Table 4.2). Infant regulation of state was negatively correlated with the AUCi ($\rho = -.384$, $p = .005$), and the Morning Slope ($\rho = -.326$, $p = .010$). However, after correcting for multiple comparisons using FDR, these relationships were no longer significant.

4.3.2 Maternal antenatal cortisol and the NBAS supplementary items.

There were no significant correlations between any of the maternal cortisol indices during pregnancy and the supplementary items of the NBAS (Table 4.1).

Table 4.1: Associations between antenatal cortisol indices and the five NBAS clusters prior to adjusting for multiple comparisons.

		1	2	3	4	5	6	7	8	9	10
1	AUCg	-									
2	AUCi	.108	-								
3	Morning Slope	-.113	.849**	-							
4	PM Avg	.059	-.049	.030	-						
5	Diurnal Slope	-.860**	-.318**	-.080	.170	-					
6	Orientation	.087	-.172	-.217	-.045	.126	-				
7	Motor	-.033	-.106	-.134	-.012	.002	.270*	-			
8	Range of State	-.055	-.048	-.093	-.146	-.154	-.162	.035	-		
9	Regulation of State	-.115	-.384**	-.326*	-.082	.112	.155	.206	-.231	-	
10	Autonomic	-.102	-.042	-.039	.249	.130	.163	.161	-.216	.276*	-

* $p < .05$, ** $p < .01$, *** $p < .001$

AUCg: AUC with respect to ground; AUCi: AUC with respect to increase; PM Avg: Mean evening cortisol

Table 4.2: Associations between antenatal cortisol indices and the supplementary items of the NBAS.

	1	2	3	4	5	6	7	8	9	10	11	12
1 AUCg	-											
2 AUCi	.108	-										
3 Morning Slope	-.113	.849**	-									
4 PM Avg	.059	-.049	.030	-								
5 Diurnal Slope	-.860**	-.318**	-.080	.170	-							
6 Quality of Alertness	.141	.069	-.055	.058	.056	-						
7 Cost of Attention	.085	.080	.054	-.016	.060	.725**	-					
8 Examiner Facilitation	.090	-.111	-.078	.042	.113	.746**	.796**	-				
9 General Irritability	.040	-.058	.018	.029	.131	.546**	.691**	.730**	-			
10 Robustness and Endurance	.168	.024	-.043	.026	-.083	.616**	.633**	.655**	.587**	-		
11 State Regulation	.134	-.146	-.165	.187	.087	.662**	.649**	.695**	.694**	.611**	-	
12 Examiner's Emotional Response	.170	.020	-.030	-.004	-.040	.697**	.710**	.737**	.574**	.567**	.672**	-

* $p < .05$, ** $p < .01$, *** $p < .001$ AUCg: AUC with respect to ground; AUCi: AUC with respect to increase; PM Avg: Mean evening cortisol

4.3.3 Maternal antenatal cortisol and the subscales of the BSID.

Pearson's correlations were conducted to assess the relationship between maternal cortisol during pregnancy and the cognitive, language and motor scales of the BSID at six and twelve months (Table 4.2). Mean maternal evening cortisol (PM Avg) was negatively associated with cognitive development at six months ($r=-.298$, $p=.008$). At twelve months there was a statistically significant positive correlation between motor development and AUCi ($r=.245$, $p=.042$). None of the above associations between maternal antenatal cortisol and the cognitive or motor scales of the BSID were significant following correction for multiple comparisons using FDR.

Pearson correlations indicated no statistically significant correlations between any of the maternal cortisol indices during pregnancy and the scores on the social-emotional scale or the adaptive behaviour questionnaire of the BSID at two, six or twelve months (Table 4.3).

Table 4.3: Associations between antenatal cortisol indices and the cognitive, language and motor subscales of the BSID at 6 and 12 months

		1	2	3	4	5	6	7	8	9	10	11
1	AUCg	-										
2	AUCi	.323**	-									
3	Morning Slope	.014	.752**	-								
4	PM Avg	.217	.034	.048	-							
5	Diurnal Slope	-.197	-.061	.005	.181	-						
6	6m Cognitive	.098	.206	.062	-.298**	-.081	-					
7	6m Language	-.043	-.065	-.228	-.072	-.027	.279**	-				
8	6m Motor	-.068	-.116	.012	-.139	-.191	.318**	.289**	-			
9	12m Cognitive	.228	.147	.003	-.099	.048	.045	-.105	-.002	-		
10	12 Language	.069	.219	.230	-.064	-.135	.124	.060	.199	.233*	-	
11	12m Motor	.146	.327*	.226	-.078	.012	.111	.033	.298**	.462**	.312**	-

* $p < .05$, ** $p < .01$, *** $p < .001$ AUCg: AUC with respect to ground; AUCi: AUC with respect to increase; PM Avg: Mean evening cortisol

Table 4.4: Associations between antenatal cortisol indices and the social-emotional and adaptive behaviour subscales of the BSID at 2, 6 and 12 months.

	1	2	3	4	5	6	7	8	9	10	11
1 AUCg	-										
2 AUCi	.323**	-									
3 Morning Slope	.014	.752**	-								
4 PM Avg	.217	.034	.048	-							
5 Diurnal Slope	-.197	-.061	.005	.181	-						
6 2m Social-Emotional	-.091	-.039	-.068	-.037	.095	-					
7 2m Adaptive Behaviour	-.151	-.065	-.039	-.185	.029	.598**	-				
8 6m Social-Emotional	-.027	.121	.093	.191	-.133	.427**	.299*	-			
9 6m Adaptive Behaviour	-.160	-.064	-.103	-.086	-.109	.398**	.668**	.254*	-		
10 12m Social-Emotional	.038	.197	.064	-.089	-.005	.519**	.185	.501**	.161	-	
11 12m Adaptive Behaviour	-.072	.121	-.034	-.161	.026	.259*	.453**	.125	.523**	.180	-

* $p < .05$, ** $p < .01$, *** $p < .001$ AUCg: AUC with respect to ground; AUCi: AUC with respect to increase; PM Avg: Mean evening cortisol

4.4 Discussion

The aim of this study was to assess the relationship between maternal antenatal diurnal cortisol and infant neurodevelopmental outcome during the first postnatal year. I was hypothesised that higher levels of maternal cortisol would be negatively associated with infant scores on the NBAS at two months and subscales of the BSID at six and twelve months. At two months there were significant negative associations between two measures of the CAR (AUCi and Morning Slope) and the *Regulation of State* cluster of the NBAS. At six months mean evening cortisol (PM Avg) was negatively associated with infant cognitive development. At twelve months there was a positive association between a measure of the CAR (AUCi) and infant motor development. However, after correcting for multiple comparisons using the FDR method, none of the above correlations remained statistically significant.

4.4.1 Antenatal Cortisol and the Neurobehavioral Development

At two months, the *Regulation of State* cluster of the NBAS was negatively associated with two of the cortisol indices representing aspects of maternal CAR during pregnancy: the AUCi and the Morning Slope. The regulation of state cluster is a measure of the infant's ability to regulate their behavioural state in the face of increasing levels of stimulation across the course of the NBAS assessment. The data in this study indicate that a greater change in cortisol over the three morning time-points or a more reactive maternal cortisol awakening response during pregnancy is associated with a decreased ability of an infant to regulate their state during the NBAS assessment.

The literature consists of a handful of studies that have previously investigated the relationship between maternal cortisol during pregnancy and infant behaviour with even fewer investigating specific aspects of diurnal cortisol such as the cortisol awakening response. Bolten et al (2013) previously reported that maternal antenatal CAR predicted infant self-quieting behaviour, an aspect of infant regulation of state, but only through an interaction with infant behavioural reactivity. Thus no direct effect of

maternal antenatal CAR on infant self-quieting was reported. Furthermore De Weerth, Buitelaar & Biegers (2013) reported that infants of mothers with a higher CAR in pregnancy demonstrated no habituation in cortisol stress response to a repeated stressor at 9 months. De Weerth et al (2013) did not measure infant self-regulatory behaviours but it is possible that the lack of habituation could be due to the infant's inability to self-regulate to the stressor that was presented. The results of this study are in line with what has previously been reported indicating that there is a potential programming effect of maternal antenatal cortisol levels which is negatively associated with infant self-regulatory ability.

It is also important to note that there were no significant correlations between the maternal measures of cortisol and the remaining NBAS clusters or supplementary items. The supplementary items of the NBAS provide summary scores of the infants' behaviour and are designed to capture the more subtle signs of stress that may not be captured by the NBAS clusters. The results of the current study are also somewhat contrary to the findings above such as that of De Weerth et al (2003) who reported that higher antenatal cortisol was associated with increased crying and fussing behaviour in infants. This study is also contrary to the findings of Braithwaite et al (2017) who reported that maternal antenatal waking cortisol predicted infant negative emotionality in a sex-specific manner. This study used the irritability item from the supplementary scale of the NBAS and found that female infants exposed to high cortisol levels demonstrated more negative emotionality whereas male infants demonstrated less negative emotionality. Davis et al (2007) found that only elevated cortisol at 30-32 weeks gestation was associated with increased infant negativity and there was no association with maternal cortisol and infant negative affect measured earlier in pregnancy. Within the current study women in both their second and third trimester were recruited (Range 18-34 weeks). Due to the changing nature of the maternal HPA axis across pregnancy, particularly from 25 weeks gestation onwards, grouping these

women within the same analysis may have obscured additional associations with the infant behavioural measures.

Infant self-regulation ability may also be a reflection of the infant's current cortisol levels such that poorer infant self-regulation may be associated with greater cortisol reactivity in response to stress (Keenan et al., 2003). It is possible that there may be an indirect relationship or an interaction effect between higher antenatal cortisol, infant cortisol and infant behaviour in a similar manner to that reported by Bolten et al (2013) with regards to infant reactivity. It is also possible that the relationship between CAR reactivity and infant self-regulation is partly moderated by another mechanism. Infant self-regulation develops in mutually regulated parent-infant interactions characterised by affective matching (Gianino & Tronick, 1988). Thus there may be an influential role of the mother's behaviour and her responsiveness to her infant during mother-infant interactions. Future studies should investigate the moderation effect of infant factors such as cortisol reactivity or indeed maternal factors as mentioned above on infant outcomes in this manner.

4.4.2 Antenatal Cortisol and the Bayley scales of Infant development

At six months antenatal mean evening cortisol (PM Avg) was negatively associated with the cognitive subscale of the BSID. At twelve months, there was a significant positive association between cortisol change across the morning time-points (AUCi) and infant motor development at twelve months.

Within the literature investigating the impact of antenatal cortisol on infant neurodevelopment, cognitive development is the most commonly studied aspect of infant outcome. Although this study is the first to report on the impact of antenatal evening cortisol levels, the negative association between antenatal cortisol and cognitive development scores has been previously reported by a number of authors (e.g. LeWinn et al., 2009; Bergman et al., 2010; Buitelaar et al., 2003). However Davis et

al (2010) reported that the relationship between higher maternal cortisol and infant cognitive development differed according to whether the exposure was early or late in gestation. Davis et al (2010) reported that early exposure of the fetus to higher antenatal cortisol levels was associated with lower cognitive development scores whereas there was an association between exposure to higher cortisol later in gestation (38 weeks) with higher cognitive developmental scores. This pattern fits with what is known about the maternal HPA axis during pregnancy in that as the fetus approaches full-term maternal cortisol continues to increase while 11 β HSD-2 levels drop which leads to a surge in fetal exposure to cortisol in late gestation that facilitates fetal tissue maturation (Xiong & Zhang, 2014). Therefore the finding that exposure to elevated levels of cortisol earlier in gestation is associated with lower cognitive score is consistent with the findings of the current study. However, it is also important to note that this association did not remain at twelve months as there was no relationship between any of the cortisol indices and cognitive development at this time point. As mentioned above in relation to the infant's ability to self-regulate, it is possible that infant cognitive development was influenced by elements of the postnatal environment such as supportive maternal behaviour. Again, this question will be addressed later in this thesis.

Little is known about the relationships between maternal antenatal cortisol and infant motor development as this relationship has seldom been reported on in the literature. Within this study the positive association between antenatal cortisol and infant motor development was unexpected. A detailed literature search indicates that there has only been one previous study which investigated the relationship between antenatal cortisol and motor development. Buitelaar et al (2003) found antenatal cortisol to be negatively associated with infant motor development at three and eight months which is contrary to what was found in this study.

According to the results reported above, it is possible that cortisol secretion has a different impact on fetal development depending on the nature of the diurnal

pattern of the mother. Within this study, higher morning cortisol had a positive association with infant motor development whereas higher evening cortisol had a negative association with cognitive development. Although there were no associations between any of the cortisol indices and measures of antenatal mood in this study, higher evening cortisol in pregnancy has previously been reported in mothers with depression (O'Keane et al., 2011). A flatter CAR has also been associated with experiencing stressful life events during pregnancy (Obel et al., 2005) and in mothers with higher trait anxiety. Thus a more responsive CAR may indicate lower anxiety or stress during pregnancy and may be one explanation as to why there was a positive association between the measures of the maternal CAR and infant language and motor development. These findings emphasise the need for future studies to investigate the diurnal nature of cortisol rather than cortisol measured at one point during one day. Incorporating diurnal measures of cortisol may provide a clearer picture as to what aspects of the diurnal nature of cortisol secretion are associated in fetal programming of later infant neurodevelopment.

4.4.3 Antenatal Cortisol and the Social-Emotional and Adaptive Behaviour Scales

This study found no associations between any of the antenatal cortisol indices and the Social-Emotional scale or Adaptive Behaviour Scale of the BSID. There are no previous reported studies assessing the relationship between antenatal cortisol with these specific measures. However, the SE scale measures functional emotional skills including self-regulation and engagement with others which may overlap with other measures of infant temperament completed by the mother such as the Infant Behavior Questionnaire (Rothbart, 1981) or the Infant Characteristics Questionnaire (Bates, Freeland & Lounsbury, 1979). Similar to this study, Gutteling et al (2006) found that antenatal cortisol was unrelated to infant temperament measured by the Infant Characteristics Questionnaire. Moreover Baibarazova et al (2012) reported that

antenatal cortisol was indirectly related to negative temperament through an interaction with infant birthweight. Lastly, Davis et al (2007) found a relationship between elevated cortisol at 30-32 weeks but not earlier in pregnancy with infant negative reactivity. Due to the inconsistencies reported within the literature, there is no consensus as to whether there is a direct association between antenatal cortisol and infant temperament or infant social-emotional development. However, it is possible that this relationship is dependent on an interaction with other factors such as infant sex, birthweight, genetic influences or HPA axis activity or indeed, as mentioned previously, supportive or sensitive maternal behaviour. Although no associations were found between the cortisol indices and the SE or AB scales, an important point to consider is maternal mood at the time of completing the questionnaires. Maternal depressed mood can impact how a mother responds to questionnaires relating to her infants behaviour which can contribute to bias in reports of child outcome (Waters et al., 2014). In light of the above, infant measures that rely on maternal report should be interpreted with caution.

4.4.4 Antenatal Cortisol Measurement

As alluded to in the introduction to this chapter, the literature investigating the impact of antenatal cortisol levels on infant outcomes reports numerous inconsistent and conflicting findings. It is very likely that this is a reflection of both the diverse methodology used in the measurement of cortisol and the choice of indices used to compare cortisol with the various outcome measures. This makes it very difficult to compare the findings of this study, or indeed any of the studies previously mentioned with each other. The diverse nature of cortisol measurement, in particular the cortisol awakening response, has also been raised as issue by the *International Society of Psychoneuroendocrinology* who proposed best practice guidelines on how to measure and report the cortisol awakening response (CAR) in order to ensure that research using

this measure produces more reliable and reproducible results (Stalder et al., 2015). Both the cortisol awakening response and diurnal slope have been established as core indices of cortisol measurement in the literature outside of pregnancy and it is necessary that these standards and protocols are also adopted for studies investigating maternal cortisol in the antenatal period also.

Specific to this study, the manner in which our samples were collected may have introduced elements of sampling error into the sample. Firstly, the mothers collected their saliva samples by themselves in their homes, therefore it is possible that the samples were subject to measurement errors due to inaccuracies in the timing at which the sample was collected or in participants failing to follow the protocol correctly (e.g. no eating or drinking before collection of samples). Future studies could incorporate the use of electronic devices to remind mothers to collect their sample or to accurately record when the sample was collected so to identify any deviations from the specified protocol. Secondly, the CAR has been reported to peak between 30-45 minutes after waking (Clow et al., 2004). Secondly, the Cortisol Awakening Response is known to be influenced by situational factors. For example, the CAR is reported to be higher on workdays than weekend days (Kunz-Ebrecht et al., 2004). To minimise potential variance in future studies, the day of the week in which cortisol is measured should be considered as well as sampling across a number of days in order to gain a more robust measure of the response for each participant (Hellhammer et al., 2007).

Lastly this study did not control for any potential confounding variables within the analysis. Preliminary analyses which included potential confounders such as parity, maternal postnatal depression score and gestational age at birth, resulted in a dramatically reduced sample size due to missing data, thus to maintain statistical power, the analyses were not adjusted for covariates.

4.4.5 Conclusions

At two months, there were significant negative associations between measures of the Cortisol Awakening Response and the regulation of state cluster of the NBAS. At six months, mean evening cortisol (PM Avg) was negatively associated with infant cognitive development and diurnal slope was negatively associated with infant adaptive behaviour. Lastly, at twelve months there was a positive association between CAR measures and infant motor development. The results of this study indicate that cortisol may play a role in the fetal programming of a number of aspects of infant development, thus contributing to the evidence supporting the DOHaD hypothesis. However these results need to be interpreted with caution as none of the above correlations remained statistically significant after correcting for multiple comparisons. Due to the inconsistencies within the literature investigating the relationship between antenatal cortisol it is of key importance that future research adopts a more consistent protocol for the measurement of cortisol in the antenatal period. This will allow for more robust results and greater ease of comparison between studies. The cortisol awakening response and diurnal slope provide a picture of daily cortisol secretion and the cortisol response to stress. It is recommended that future studies use the CAR and diurnal measures as higher levels of cortisol at different points in the diurnal curve may have different consequences on the developing fetus.

Chapter 5

Associations between maternal antenatal and postnatal depression with maternal-infant interactive behaviour

5.1. Introduction

According to the Developmental Origins of Health and Disease (DOHaD) hypothesis, early life experiences comprise one pathway through which an individual's susceptibility to psychopathology later in life is increased. Disruption to maternal caregiving behaviour due to the onset of postnatal depression or as a result of continuing depressive symptoms from the antenatal period can play a significant role in later adverse infant and child developmental outcomes (Kaplan et al., 2012).

Maternal sensitivity is a construct often used to describe a mother who can respond appropriately to her infant and can provide their infant or child with prompt, adequate and appropriate care (Ainsworth, Bell & Stayton, 1974). Within a research context, maternal sensitivity is representative of a global or 'macro' level measure of maternal behaviour towards her infant, typically represented by a single score which is indicative of overall higher or lower degrees of sensitive care. In contrast, 'micro' level coding involves identifying specific target behaviours which mothers may potentially exhibit during an interaction with her infant and involves coding their frequency or the sequential pattern in which they occur within small time fragments (Mesman, 2010). Macro level coding is advantageous in that it captures the larger context of maternal behaviour with regards to how the infant perceives that behaviour (Mesman, 2010; Chorney et al., 2015). However, in designing and implementing therapeutic interventions with the purpose of improving maternal caregiving behaviour, it is necessary to gain an understanding of the 'micro level' or specific behaviours that are impacted in this context so that interventions can target specific maladaptive behaviours which may have consequences for infant developmental outcomes (Cordes et al., 2017).

5.1.1 Maternal and infant matched affective expression

Maternal-Infant affective matching is a dyadic measure of interactive coordination where the mother and her infant are in the same affective state at the same time (Moore & Calkins, 2004). Affective synchrony within the mother-infant relationship is vitally important in supporting the infant in their social-emotional development as well as the ability to self-regulate. Both antenatal and postnatal depression have been associated with corresponding difficulties in infant self-regulation strategies (Kaplan et al., 2008), therefore, mother-infant affective matching has frequently been studied in this context as a potential mechanism through which these difficulties can occur.

Within the literature focusing on depression during the perinatal period, mother-infant affective matching has primarily been observed across two differing interactional contexts: the Still-Face procedure (Tronick et al., 1978) and unstructured play. Unstructured or 'free play' observations are recorded either within a laboratory or home setting and consist of scenarios in which the mother is given no specific instructions other than to 'play with her infant as she typically would'. Frequently, infants are placed in an infant car seat or high-chair in a face to face scenario with their mother (e.g Cohn et al., 1990; Goodman et al., 2017). However, often mothers are also given no specific instructions as to how to position their infant (Kim et al., 2012; Radke-Yarrow et al., 1993). Observational periods vary in duration ranging from three minutes (Field et al., 1990; Cohn et al., 1990) to two hours at a time (Bell et al., 2004).

Matched-affect in mother-infant dyads in the context of antenatal or postnatal depression demonstrate conflicting results. Postnatal depression has been associated with lower levels of overall affective matching (Field et al., 1990) and lower levels of matched positive affect (Bell et al., 2004). However further studies have also reported higher affective matching (Beebe et al., 2008) while some have reported no differences at all (Cohn et al., 1990). Lastly in the only study to have reported the relationship between antenatal depression and matched affect, Goodman and colleagues (2017)

reported an association between antenatal depression and lower dyadic affective matching but no association between postnatal depression and shared mother-infant affect.

An additional context in which maternal-infant affective matching is typically observed is during the 'Still-Face Procedure' (Tronick et al., 1978) an experimental procedure consisting of three specific phases in a face-to-face interaction between the mother and her infant. Firstly, the mother is instructed to interact with her infant as she usually would. This phase is followed by a period where the mother remains in front of the infant but adopts a still, unresponsive face. The mother is then instructed to resume a normal interaction with the infant in a phase often called the 'reunion'. In studies utilising the Still-Face Procedure, Reck and colleagues (2011) reported higher degrees of matched positive affect in control participants and found that depressed dyads took longer to repair mismatched states to return to a positive matching states.

5.1.2 Maternal Linguistic Complexity and Vocal Responsiveness

Maternal affective expression and the ability to synchronise this aspect of behaviour with that of her infant are considered vital in supporting an infant's self-regulatory capacities. However, maternal speech is also considered a core element of this affective expression and plays an important role in facilitating the mother-infant relationship while also supporting emerging infant cognitive, social-emotional and particularly language development within a child's early years. Research focusing on the fundamental frequency modulation of the exaggerated intonational features of infant directed speech indicates that the speech of mothers with depression is typically flatter with less prosodic variation (Kaplan et al., 2001). This has corresponding implications for infant behaviour and language development which are facilitated by the pitch variation in mothers' infant directed speech (Porritt et al., 2014). However, less is known about the impact of maternal depression on other important elements of

maternal speech quality such as the syntactic complexity, typically denoted by a mothers mean length of utterance (MLU) a measure of the average number of morphemes per maternal utterance (Sandbank & Yoder, 2016), and the complexity of maternal linguistic input which are both reported to play a role in children's language development (Rowe, 2012).

Interestingly, the majority of studies which have investigated the impact of postnatal depression on the frequency of maternal utterances and the syntactic and lexical quality report no differences between depressed mothers and controls (Pound et al., 1988; Righetti-Veltema et al., 2002; Cornish et al., 2008) or mothers with a history of depression and controls (Murray et al., 1993). In fact, a detailed search of the literature found only one study that reported reduced vocal frequency in mothers with depression (Breznitz & Sherman, 1987). Even fewer studies have reported on maternal postnatal depression and the corresponding impact on a mother's promptness or frequency of vocal responses towards her infant. Mothers with depression have been reported to be slower to respond to their infant's vocalisations (Bettes, 1988; Breznitz & Sherman, 1987) and have longer and more variable switching pauses, defined as the duration of silence after the infant stops vocalising and the mother begins, during maternal-infant vocal interactions (Zlochower & Cohn, 1996).

5.1.3 Study Outline

This study aimed to assess the impact of a clinical diagnosis of depression during pregnancy on maternal interactive behaviours during the first postnatal year. Three groups of women were recruited to the study: a group of mothers who had a clinical diagnosis of Major Depressive Disorder during pregnancy, a group of mothers with a history of one or more episodes of Major Depressive Disorder who were currently euthymic and a group of matched controls with no current psychiatric disorders and no history of depression. Mothers and their infants were followed up at two, six and twelve months post-partum and a short unstructured interaction between each mother and

her infant was recorded. Each video clip was coded for the proportion of time mother and infant both exhibited positive, neutral or negative affect. Maternal responses to infant vocalisations were also coded, and mean maternal response latency was calculated from each recording. Lastly, all clips were transcribed and maternal mean length of utterance (MLU) and lexical diversity (*vocd*) were calculated from each transcript.

Hypotheses

- 1) Mothers in the Depressed group would exhibit lower levels of linguistic input during interactions with their infants at two, six and twelve months compared with mothers in the History and Control groups.
- 2) Mothers in the Depressed group would exhibit longer vocal response latencies and switching pause durations in response to their infants' vocalisations at two, six and twelve months compared with mothers in the History and Control groups.
- 3) Mothers in the Depressed group would demonstrate less positive affect and more neutral and negative affect during interactions with their infants at two, six and twelve months compared with mothers in the History and Control groups.
- 4) Mother-infant dyads in the Depressed group would demonstrate less matched positive, neutral and overall affect during interactions with their infants at two, six and twelve months compared with those in the History and Control groups.
- 5) Current postnatal depression would be negatively associated with maternal linguistic input, vocal response latencies and total matched affect at two, six and twelve months within the sample as a whole.

5.2 Method

5.2.1. Participants

Participants were recruited from the Perinatal Psychiatry services and antenatal booking clinics within the National Maternity Hospital, the Coombe Women and Infants University Hospital and the Rotunda Hospital in Dublin. Participants in their second or third trimester who met the inclusion and exclusion criteria were clinically assessed by Dr. Chai Jairaj, a research registrar in Psychiatry. Participants were recruited into a depressed, history or control group. Demographic data for the whole sample is presented in Section 3.4.2 of Chapter 3.

5.2.2 Measures

Maternal Demographic Characteristics

Maternal demographic information was recorded at the time of recruitment interview and included the following variables: maternal age, ethnicity, education, employment status and marital status.

Maternal health behaviours and obstetric factors

Maternal antidepressant medication and current levels of cigarette and alcohol consumption were recorded. Details pertaining to the mother's obstetric history and current pregnancy were also recorded. These variables included: gravidity, parity, and any previous obstetric complications.

Maternal Clinical Measures

The MINI International Neuropsychiatric Interview (M.I.N.I.) (Sheehan et al., 1998) and the Hamilton Rating Scale for Depression (HAM-D) (Hamilton, 1960) were completed by Dr. Chaitra Jairaj at recruitment. Mothers also completed the Center for Epidemiologic

Studies: Depression Scale (CES-D) (Radloff, 1977) and Perceived Stress Scale (PSS) (Cohen, Kamarck & Mermelstein, 1983) on recruitment to the study and at two, six and twelve months postpartum.

Infant Birth Characteristics

Infant birth details were obtained from participant medical records at each maternity hospital. In cases where this data was not available, the information was collected from the mother. Information on the mode of onset of labour, delivery method, infant gestational age at birth, weight at birth, one minute and five minute APGAR scores and head circumference were collected. Additional information on infant characteristics such as current weight, feeding method and hours of childcare per week were provided by the mother at the two, six and twelve month time points.

5.2.3 Maternal-Infant Interaction

Video Recordings

Following the completion of the developmental assessment at each time point a three minute video clip of a free play interaction between each mother and her infant was recorded using a NIKON D3100, a 14.2-megapixel DX format DSLR camera. Each mother was instructed to 'Play or interact with your baby as you usually would. You can use toys or not as you choose'. Mothers were allowed to choose how they would position their baby and what toys they would use, if any.

Affect

The videos were coded for affect by three coders who were completely blind to the purpose of the study. All coding was completed using INTERACT™ software (Mangold, 2006). Clips were coded for both maternal and infant moment to moment affective behaviour in separate phases. For both mother and infant, affective behaviour was coded as either positive, neutral or negative using a coding system (Appendix x) which outlined behavioural signifiers for each classification of affective behaviour. This coding scheme was designed by the author along with Dr. Elizabeth Nixon and Dr. Jean Quigley of the School of Psychology, Trinity College. The proportion of time that mother and infant displayed either positive, neutral or negative affect was recorded as a percentage resulting in a possible six variables for each mother-infant dyad. Four additional variables representing the proportion of time that mother and infant were matched for neutral, positive and negative affect and a composite variable comprising the total proportion of time that mothers and infants were matched for affect were also recorded. This variable was obtained through the co-occurrence function within INTERACT which searches for classes; situations where mother or infant are displaying positive, neutral or negative affect; that occur simultaneously for both mother and infant. INTERACT then calculates the total percentage of co-occurring events for each class separately. This comprises the variables of total matched neutral, negative or positive affect. These percentages were then added to create the percentage of time per clip that each dyad were matched for overall affect.

Maternal mean response latency and switching pause duration

The videos were coded for infant and maternal vocalisations by three coders who were completely blind to the purpose of the study. Coding for this variable was completed using INTERACT™ software (Mangold, 2006). In the first phase, any effortful or speech-like non-distress vocalisation made by the infant was coded. Infant sounds such as

crying, fussing, laughing or other vegetative sounds were not coded. In the next phase any maternal vocalisations uttered within 5 seconds of the onset of an infant vocalisation were coded. Maternal sounds such as laughing or noises such as kisses or 'blowing raspberries' were not coded. Vocalisations made outside of the 5 second window were designated as a non-contingent vocal response. Two variables were obtained from this data: maternal mean response latency and switching pause duration. Mean maternal response latency for each participant was calculated by averaging the duration of time between the onset of the infant vocalisation and the onset of the mother's vocalisation. Switching pause duration was calculated by averaging the duration of time between the offset of an infant vocalisation and the onset of the mother's vocalisation for each participant. If the infant made no vocal overtures towards their mother during the three minute video-clip no data were coded for this clip. At two months there were no vocal overtures from eight of the infants [Depressed=1, History=3, Control=4], at six months there were no vocal overtures from two of the infants [Depressed=1, History=1] and furthermore at twelve months there were no vocal overtures from two of the infants [History=1, Control=1].

Maternal mean length of utterance (MLU) and lexical diversity (vocd)

All maternal vocalisations observed in the video clips were transcribed using CLAN (MacWhinney, 2000) by the author. Preliminary checks using the CHECK and MOR utilities were completed to ensure that the transcripts were set up correctly and to ensure that words were transcribed in the correct morphological structure. Two variables were obtained from the transcripts using the KIDEVAL utility within the CLAN program: Mean Length of Utterance (MLU) and lexical diversity (*vocd*).

Maternal Mean Length of Utterance (MLU) is a measure of maternal language complexity and is often used as a proxy measure of grammatical input (Sandbank & Yoder, 2016). MLU is denoted by the average number of morphemes per utterance of

the mother during a sample of speech. *D* (Richards & Malvern, 1997) is a measure of vocal diversity which is based on the entire sample of words produced by the mother within a sample of speech. It is advantageous over other measures of vocal diversity such as the Type-Token Ratio, calculated by dividing the total number of unique words used by the total of words spoken, as it allows comparisons of speech samples of varying sizes. Values for both MLU and *D (vocd)* were obtained from each transcript at two, six and twelve months.

Inter-Rater Reliability

Inter-rater reliability for the affect and vocalisation variables was completed by three research assistants who were completely blind to the purpose of the study. Inter-rater reliability was calculated for 16-26% of the video clips. Time-unit *kappa* values reflecting the extent of agreement for positive, neutral and negative affect for both mother and infant are presented in Chapter 2, Table 2.5. Percentage agreement for the mother-infant vocalisations are also presented in Chapter 2, Table 2.5.

Interpretation of the value of *kappa* is dependent on the number of categories that are coded. Within this study there were three potential categories in which affect was coded for both mother and infant positive, neutral or negative, and whose frequencies were highly variable. Therefore *kappa* scores above .83, .68, .55 represent observer reliability of 95%, 90% and 85% accurate respectively (Bakeman and Quera, 2011).

Missing and Excluded Video Recordings

A number of mothers within this sample were not native English speakers and spoke to their infants in a language other than English. These clips were not transcribed and thus MLU or *vocd* was not measured in these participants. In addition, a number of video clips are missing from the 2 month time-point for two reasons: (i) infants born in the

initial part of the study did not partake in the developmental assessments as this arm of the study had not commenced yet and (ii) a number of infants were asleep at the time of the video recording. The participants for which interaction data were available is presented in Chapter 2, Table 2.4

5.2.4 Statistical Analyses

All data were analysed using SPSS (Version 24, IBM). All data were firstly assessed for normality using the Shapiro-Wilk test. Due to the presence of positive skewness in the variables measuring affect, these variables were transformed using the ARCSINE transformation (Cohen & Cohen, 1983). This was completed in order to approximate a normal distribution and allow for general linear model analysis. Continuous data are presented as mean (M) and standard deviation (SD). All data are reported to two decimal places with the exception of p values which are reported to three decimal places. Threshold of significance is set at 0.05 for all analyses.

Normally distributed data were analysed using one way analysis of variance (ANOVA) or multiple linear regression as appropriate. The Tukey HSD test was used in post-hoc analysis of group differences following ANOVA. Non-parametric data were analysed using the Kruskal-Wallis Test for Independent samples and post-hoc tests were carried out using Mann-Whitney U tests. Fisher's Exact Test was used to analyse categorical data when the cell count was less than 5. For interpretation of the results of χ^2 test or Fisher exact test standardised residuals were examined. A standardised residual of ≤ 2 indicates that the observed frequency of a given variable is lower than the expected frequency. A residual of ≥ 2 indicates that the observed frequency is significantly higher than the expected frequency (Field, 2013).

Mediation analysis was conducted using Model 4 of PROCESS, an SPSS macro (Hayes, 2013). PROCESS uses a regression based, path analytical framework to assess the relationship between a predictor variable and an outcome variable through their relationship to a third, mediating, variable (Field, 2013). Mediation analyses were

utilised to assess the potential indirect effect of antenatal depression on maternal speech complexity through maternal concurrent depression. Separate models were conducted for both maternal MLU and *vocd* at each time-point. In each model, either MLU or *vocd* were entered as the outcome variable, antenatal depression as the independent variable and concurrent maternal depression as the mediating variable. A nonparametric bootstrapping method of 10000 samples and a confidence interval of 95% was used. An indirect association is considered to be significant if the 95% confidence interval does not include zero.

Maternal education and parity were chosen as covariates for the data analysis. Parity was chosen as a covariate as a larger family size has been reported to reduce the quality and quantity of parent-infant interactions (Steelman et al., 2002). Maternal education was also chosen as a covariate as early maternal dialogue with her infant has been shown to be partly a function of the mother's educational level (Rowe, 2012).

5.3 Results

5.3.1 Group Comparisons

Group Comparisons of maternal mean length of utterance (MLU) and lexical diversity (vocd)

Descriptive data for the measures of maternal MLU and *vocd* for each group are presented in Table 5.1. A one way analysis of variance indicated no significant group differences between the Depressed, History or Control groups for either maternal MLU or *vocd* at two, six or twelve months.

Group Comparisons of Maternal Vocal Response Latency (RL) and Switching Pause (SP)

Descriptive data for the measures of maternal vocal response latency and switching pause duration in milliseconds for each group are presented in Table 5.2. A one way analysis of variance indicated no significant differences between the Depressed, History and Control groups for maternal response latency at two, six or twelve months. A Kruskal-Wallis test indicated no significant differences between the Depressed, History or Control groups for duration of maternal switching pause at two, six or twelve months.

Table 5.1: Descriptive data and group comparisons for maternal mean length of utterance (MLU) and lexical complexity (*vocd*) at two, six and twelve months.

	Depressed	History	Control	
	Mean (SD)	Mean (SD)	Mean (SD)	Statistic, <i>p</i> value
2 Months				
MLU	3.93 (.87)	3.99 (1.14)	4.63 (1.07)	$F(2, 53)=2.711, p=.076$
VOCD	32.84 (6.74)	28.13 (11.65)	31.75 (11.24)	$F(2, 51)=1.463, p=.241$
6 Months				
MLU	4.03 (1.02)	4.29 (1.17)	4.39 (1.03)	$F(2, 69)=2.473, p=.092$
VOCD	34.17 (12.17)	29.16 (11.28)	31.92 (11.52)	$F(2, 65)=.891, p=.416$
12 Months				
MLU	4.51 (1.19)	4.51 (1.33)	4.7 (1.2)	$F(2, 68)=1.074, p=.347$
VOCD	32.41 (12.42)	27.5 (11.84)	31.00 (12.12)	$F(2, 66)=1.282, p=.284$

Table 5.2: Descriptive data and group comparisons for maternal response latency (RL) and switching pause (SP) duration in milliseconds at two, six and twelve months.

	Depressed	History	Control	
	Mean (SD)	Mean (SD)	Mean (SD)	Statistic, <i>p</i> value
2 Months				
RL	772.22 (425.18)	955.07 (417.50)	960.26 (468.86)	$F(2, 60)=.852, p=.432$
SP	551.52 (384.24)	557.97 (394.69)	800.00 (847.00)	$\chi^2 (2, 59)=.114, p=.944$
6 Months				
RL	1231.58 (490.34)	1401.24 (770.86)	1151.75 (681.44)	$F(2, 84)=1.086, p=.343$
SP	998.25 (766.30)	953.09 (670.52)	801.76 (650.89)	$\chi^2 (2, 84)=1.621, p=.445$
12 Months				
RL	1233.33 (673.01)	884.72 (568.92)	1047.62 (632.16)	$F(2, 77)=1.614, p=.206$
SP	1027.78 (939.77)	898.61 (586.93)	1094.29 (572.15)	$\chi^2 (2, 77)=2.617, p=.270$

Group Comparisons of Maternal Affect

Descriptive data for the proportion of time the mothers in each group were coded as displaying either negative, neutral or positive affect is presented in Table 5.3. One way analysis of variance indicated no significant group differences for either neutral or positive affect at two, six or twelve months. Fisher's Exact test was conducted to determine group differences in whether or not mothers displayed any negative affect within the video recorded at each time point. There were no significant differences for expression of maternal negative affect at two months [Fisher Exact Test, $p=.203$] or six months [Fisher Exact Test, $p=.388$]. However at twelve months, there was a significantly higher number of mothers who displayed negative affect in the Depressed group compared with the History or Control groups [Fisher Exact Test, $p=.036$, Standardised Residual=2.3]. In the Depressed group, 16% of the mothers displayed negative affect in comparison to 0% of the History group and 5% of the control group. Across all video clips, maternal negative affect was <2.5% of the video clip.

Table 5.3: Descriptive data with group comparisons for percentage of maternal negative, neutral and positive affect at two, six and twelve months.

	Depressed	History	Control	
	Mean (SD)	Mean (SD)	Mean (SD)	Statistic, <i>p</i> value
2 Months				
Negative	.04 (.15)	.00 (.00)	.00 (.00)	$\chi^2(2, 69)=3.929, p=.140$
Neutral	21.64 (17.61)	23.70 (25.43)	30.49 (23.65)	$F(2, 66)=.925, p=.401$
Positive	78.32 (17.63)	76.32 (25.43)	69.51 (23.65)	$F(2, 66)=.920, p=.403$
6 Months				
Negative	.24 (.86)	.14 (.54)	.30 (.77)	$\chi^2(2, 85)=1.164, p=.559$
Neutral	25.03 (20.25)	27.62 (22.09)	22.28 (17.34)	$F(2, 83)=.590, p=.557$
Positive	74.73 (20.11)	72.24 (22.15)	77.41 (17.35)	$F(2, 83)=.555, p=.576$
12 Months				
Negative	.25 (.62)	.00 (.00)	.05 (.22)	$\chi^2(2, 86)=5.423, p=.066$
Neutral	16.42 (12.70)	21.00 (20.52)	16.76 (13.71)	$F(2, 83)=.698, p=.501$
Positive	83.34 (13.01)	79.00 (20.52)	83.20 (13.80)	$F(2, 83)=.652, p=.524$

Group comparisons of infant affect

Descriptive data for the percentage of time infants in each group were coded as displaying either negative, neutral or positive affect are presented in Table 5.4.

At two months, group comparisons conducted using a Kruskal-Wallis test indicated significant group differences for infant positive affect at two months [$\chi^2 (2, 69)=6.36$, $p=.036$]. Post-hoc analyses using Mann Whitney U tests indicated that the infants in the History group displayed significantly higher positive affect in comparison to the Control group [$U=223$, $z=-2.586$, $p=.010$]. There were no significant differences between the Depressed group and either the History group [$U=174$, $z=-.030$, $p=.988$] or Control group [$U=148$, $z=-1.437$, $p=.151$]. There were no significant differences between the groups for infant neutral or negative affect at two months. At six and twelve months, there were no significant group differences for infant negative, neutral or positive affect.

Table 5.4: Descriptive data with group comparisons for percentage of infant negative, neutral and positive affect at two, six and twelve months.

Infant	Depressed	History	Control	
	Mean (SD)	Mean (SD)	Mean (SD)	Statistic, <i>p</i> value
2 Months				
Negative	15.66 (24.49)	13.88 (20.44)	28.82 (30.42)	$\chi^2 (2, 69)=4.295, p=.117$
Neutral	58.67 (25.32)	59.84 (26.14)	61.17 (28.22)	$\chi^2 (2, 69)=.208, p=.901$
Positive	25.68 (28.57)	26.28 (23.32)*	10.97 (16.37)	$\chi^2 (2, 69)=6.36, p=.036$
6 Months				
Negative	1.60 (2.68)	3.00 (9.48)	3.25 (4.84)	$\chi^2 (2, 86)=1.853, p=.396$
Neutral	62.26 (16.11)	59.10 (21.50)	59.14 (19.94)	$\chi^2 (2, 86)=.491, p=.782$
Positive	36.13 (16.83)	38.01 (21.54)	37.62 (21.07)	$\chi^2 (2, 86)=.066, p=.968$
12 Months				
Negative	3.98 (7.17)	1.72 (5.24)	.68 (2.10)	$\chi^2 (2, 86)=5.031, p=.081$
Neutral	59.52 (20.12)	57.84 (21.28)	64.72(13.99)	$\chi^2 (2, 86)=1.086, p=.581$
Positive	36.50 (21.59)	40.45 (21.04)	34.60 (13.85)	$\chi^2 (2, 86)=.558, p=.757$

**p*<.05

Group comparisons of matched maternal-infant positive, neutral and total affect.

Descriptive data for the percentage of time the mothers and infants in each group were matched for either neutral or positive affect and total matched affect are presented in Table 5.5. Group comparisons at each time-point were conducted using one ways analysis of analysis of variance (ANOVA). There were statistically significant group differences for matched positive affect at two months [$F(2, 66) = 5.581, p = .006$]. Post-hoc analyses using Tukey HSD indicated that mothers and their infants in the History group were matched for positive affect for a significantly larger proportion of time in comparison to the Control group. There were no significant differences in total matched positive affect between the Depressed group and either the History or Control groups. Group differences remained after conducting further analyses using ANCOVA, with maternal education, parity and maternal depression measured first using maternal two month HAMD score [$F(2, 46) = 4.432, p = .017$] and then two month CES-D [$F(2, 57) = 5.023, p = .010$] score as covariates.

Analysis of variance also indicated significant group differences for total overall matched affect at two months [$F(2, 66) = 4.606, p = .013$]. Post-hoc analyses using Tukey HSD indicated that mothers and their infants in the History group were matched for overall total affect for a significantly larger proportion of time in comparison with the Control group. There were no significant differences for total overall affect between the Depressed group and the History or Control groups. Group differences remained after conducting further analyses using ANCOVA, with maternal education, parity and maternal depression as covariates, measured first using maternal two month HAMD score [$F(2, 46) = 3.286, p = .046$] and then two month CES-D score [$F(2, 57) = 5.17, p = .009$]. There were no significant group differences for matched neutral affect at two months or for matched neutral, positive and total affect at six and twelve months.

Table 5.5: Descriptive data for the percentage of maternal-infant matched neutral, positive and total affect at two, six and twelve months.

	Depressed	History	Control	
	Mean (SD)	Mean (SD)	Mean (SD)	Statistic, <i>p</i> value
2 Months				
Neutral	12.49 (10.79)	18.28 (22.06)	19.65 (20.31)	F(2, 66)=.296, p=.745
Positive	21.62 (25.45)	25.11 (22.20)**	8.64 (11.57)	F(2, 66)=5.521, p=.006
Total	34.11 (22.82)	43.40 (20.51)*	26.40 (19.75)	F(2, 66)=4.606, p=.013
6 Months				
Neutral	19.35 (15.28)	20.45 (17.44)	17.45 (15.80)	F(2, 83)=.227, p=.797
Positive	30.90 (18.65)	32.14 (20.43)	32.54 (18.88)	F(2, 83)=.027, p=.973
Total	50.36 (13.07)	52.93 (15.13)	50.14 (12.00)	F(2, 82)=.381, p=.684
12 Months				
Neutral	14.62 (15.33)	14.87 (15.28)	13.28 (11.12)	F(2, 83)=.039, p=.961
Positive	30.82 (22.92)	36.95 (21.18)	30.36 (13.80)	F(2, 83)=1.117, p=.332
Total	45.61 (16.03)	51.82 (14.66)	43.69 (12.14)	F(2, 83)=.227, p=.062

**p<.01 *p<.05

5.3.2 Maternal Depression and Interactive Behaviour

Associations between maternal HAM-D and CES-D scores and MLU across the first postnatal year

Multiple regression analyses, controlling for maternal education and parity, were conducted to assess the relationship between antenatal and postnatal HAM-D and CES-D scores and maternal MLU at two, six and twelve months. Regression coefficients for HAM-D scores are presented in Table 5.6 and for CES-D scores in Table 5.7. At two months, maternal HAM-D was negatively associated with maternal MLU score [$F(3, 39) = 3.966, p = .015$]. In addition there was a statistically significant negative association between two month CES-D score and maternal MLU at six months [$F(3, 55) = 4.759, p = .005$]. Lastly, there was a statistically significant negative association between twelve month CES-D score and maternal twelve month MLU [$F(3, 58) = 5.656, p = .002$].

Associations between maternal HAM-D and CES-D scores and vocd across the first postnatal year

Multiple regression analyses, controlling for maternal education and parity, were conducted to assess the relationship between antenatal and postnatal HAM-D and CES-D scores and maternal *vocd* scores at two, six and twelve months. Regression coefficients for HAM-D scores are presented in Table 5.8 and for CES-D scores in Table 5.9. There were no statistically significant associations between maternal HAM-D and *vocd* scores at any of the time-points. However, there was a statistically significant positive association between maternal CES-D score at six months and *vocd* score at twelve months [$F(3, 49) = 2.876, p = .045$].

Table 5.6: Regression coefficients for the associations between maternal HAM-D score at each time-point and maternal MLU at two, six and twelve months.

	2 month MLU					6 month MLU					12 month MLU				
HAM-D	B	SE	beta	T	p	B	SE	beta	T	p	B	SE	beta	T	p
Pregnancy	-.029	.017	-.227	-1.696	.096	-.023	.014	-.195	-1.680	.098	-.016	.016	-.114	-.978	.332
2 months	-.104	.035	-.426	-2.970	.005	-.037	.032	-.161	-1.181	.243	-.059	.035	-.218	-1.669	.101
6 months						-.020	.034	-.112	-.595	.557	.015	.038	.073	.391	.699
12 months											-.058	.074	-.157	-.783	.442

Table 5.7: Regression coefficients for the associations between maternal CES-D score at each time-point and maternal MLU at two, six and twelve months

	2 Month MLU					6 Month MLU					12 Month MLU				
Maternal CES-D	B	SE	beta	T	p	B	SE	beta	T	p	B	SE	beta	T	p
Pregnancy	-.014	.011	-.173	-1.246	.219	-.017	.009	-.227	-1.903	.062	-.008	.010	-.090	-.757	.452
2 months	-.017	.014	-.178	-1.237	.223	-.029	.011	-.325	-2.651	.010	-.024	.013	-.229	-1.852	.069
6 months						-.017	.011	-.197	-1.542	.129	-.007	.013	-.072	-.551	.584
12 months											-.033	.013	-.292	-2.524	.014

Table 5.8: Regression coefficients for the associations between maternal HAM-D score at each time-point and maternal *vocd* at two, six and twelve months.

	2 Month <i>vocd</i>					6 Month <i>vocd</i>					12 Month <i>vocd</i>				
Maternal HAM-D	B	SE	beta	T	p	B	SE	beta	T	p	B	SE	beta	T	p
Pregnancy	.009	.171	.007	.054	.958	.095	.170	.071	.558	.579	.008	.176	.006	.047	.962
2 months	-.229	.377	-.090	-.606	.548	.570	.374	.220	1.524	.134	-.152	.390	-.056	-.390	.698
6 months						.334	.412	.168	.812	.425	.268	.414	.128	.647	.524
12 months											.938	.793	.249	1.182	.251

Table 5.9: Regression coefficients for the associations between maternal CES-D score at each time-point and maternal *vocd* at two, six and twelve months.

	2 Month <i>vocd</i>					6 Month <i>vocd</i>					12 Month <i>vocd</i>				
Maternal CES-D	B	SE	beta	T	p	B	SE	beta	T	p	B	SE	beta	T	p
Pregnancy	-.049	.108	-.060	-.448	.656	.090	.108	.109	.834	.408	.098	.111	.113	.888	.378
2 Months	-.015	.137	-.015	-.109	.914	.115	.141	.114	.819	.417	-.045	.143	-.042	-.315	.754
6 Months						-.007	.134	-.008	-.055	.956	.314	.136	.307	2.316	.025
12 Months											-.052	.149	-.045	-.349	.729

Indirect effect of antenatal depression on MLU

To test the hypothesis that maternal antenatal depressive symptoms would have an indirect effect on maternal MLU through maternal current depression, mediation analyses were conducted using the PROCESS Macro for SPSS

There was a significant indirect effect of antenatal depression on maternal MLU at two months through two month HAM-D score [indirect effect coefficient=-.0384, boot SE=.0161, Confidence interval (CI) = -.0822, -.0136].

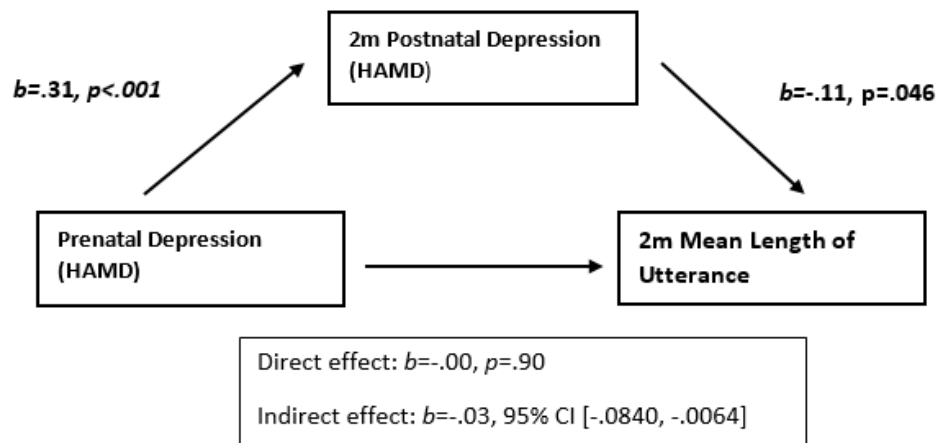


Figure 5.2: Model of maternal antenatal depression, measured by the Hamilton rating scale for Depression (HAMD) score during pregnancy as a predictor of maternal two month MLU, mediated by two month HAMD score.

There was also a significant indirect effect of antenatal depression on maternal MLU at twelve months through maternal twelve month CESD score [indirect effect coefficient=-.1059, boot SE=.0074, (CI) = -.0309, -.0019].

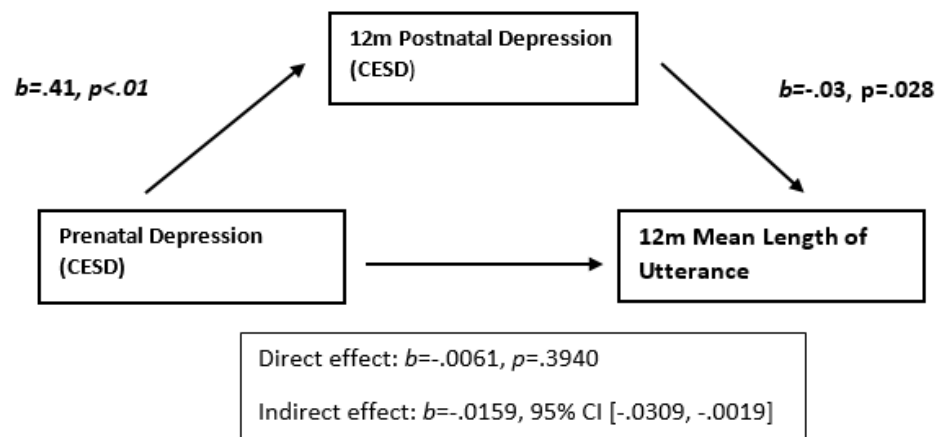


Figure 5.5: Model of maternal antenatal depression, measured by the Center for Epidemiological Studies Depression Scale (CESD) score during pregnancy as a predictor of maternal twelve month MLU, mediated by twelve month CESD score.

Indirect effect of antenatal depression on vocd

To test the hypothesis that maternal antenatal depressive symptoms would have an indirect effect on maternal *vocd* through maternal postnatal depression, mediation analyses were conducted using the PROCESS Macro for SPSS. The indirect effect of maternal antenatal depression on twelve month *vocd* score through maternal six month CES-D score was not statistically significant [indirect effect coefficient=.1464, boot SE=.1241, Confidence interval (CI) = -.0744, .4134].

Associations between maternal HAM-D and CES-D scores and Maternal Response Latency across the first postnatal year

Multiple regression analyses, controlling for parity and maternal education were conducted to assess the relationship between antenatal and postnatal HAM-D and CES-D scores and maternal response latency scores at two, six and twelve months. There were no statistically significant associations between maternal HAM-D or CES-D scores during pregnancy or two, six and twelve months postpartum and maternal response latency to infant vocalisations at two, six or twelve months.

Associations between maternal HAM-D and CES-D scores and Maternal Positive Affect across the first postnatal year

Multiple regression analyses, controlling for parity and maternal education were conducted to assess the relationship between antenatal and postnatal HAM-D and CES-D scores and proportion of maternal positive affect at two, six and twelve months. There were no statistically significant associations between maternal HAM-D or CES-D scores during pregnancy or two, six or twelve months and proportion of maternal positive affect at two, six or twelve months.

Associations between maternal HAM-D and CES-D scores and Maternal-Infant Matched Positive, Neutral and Total Affect across the first postnatal year

Multiple regression analyses, controlling for parity and maternal education were conducted to assess the relationship between antenatal and postnatal HAM-D and CES-D scores and maternal matched positive, neutral and total affect at two, six and twelve months. However, none of these regression models were statistically significant.

5.4. Discussion

The primary aim of this study was to assess the impact of a clinical diagnosis of depression during pregnancy on maternal interactive behaviour during the first postnatal year. There were no reported group differences in maternal MLU, lexical diversity, response latency to infant vocalisations or switching pause duration at any of the time-points in this study. At two months significantly higher shared positive and total affect were reported in the History group in comparison to Controls. Associations between antenatal depression and the measures of maternal interactive behaviour were not significant. However, maternal two month MLU scores was negatively associated with concurrent HAMD and CESD scores. Twelve month MLU was also negatively associated with concurrent CESD score. Maternal CESD score at six months was positively associated with *vocd* at twelve months. Although there was no direct association between maternal antenatal depression and MLU, there was an indirect association which was mediated by concurrent maternal postnatal depression at two and twelve months. Lastly at two months infants in the History group displayed higher levels of positive affect in comparison to the Control group. There were no group differences for proportion of infant affect at the six or twelve month time-points.

5.4.1 Maternal Linguistic Complexity

Maternal linguistic complexity was measured using two variables; mean length of utterance (MLU) and lexical diversity (*vocd*). Although both the Depressed and History groups had a slightly lower MLU in comparison to the Control group at each time-point, these differences were not statistically significant. Mothers in the Depressed group had slightly higher *vocd* scores at each time-point, indicative of higher linguistic diversity, however these differences were also not statistically significant. Therefore, the results of this study suggest that depression during pregnancy has no direct impact on maternal

linguistic complexity, as measured by maternal MLU and *vocd*, during the first postnatal year.

Due to the fluctuating nature of depressive symptoms within all groups across the three postnatal time-points, this study sought to determine whether there was an association between the complexity of maternal linguistic input towards her infant and concurrent maternal depression symptoms. Regression analyses indicated that there were significant negative associations between two month HAM-D and maternal MLU, two month CES-D score and six month MLU and also twelve month CES-D score and twelve month MLU. Mediation analyses indicated that there was a significant indirect effect of antenatal HAM-D score on maternal two month MLU score through two month HAM-D score. There was also a significant indirect effect of maternal antenatal CES-D score on twelve month MLU through twelve month maternal CES-D score. With regards to *vocd* scores, although there was a significant positive association between six month CES-D scores and maternal *vocd* score at twelve months, mediation analysis indicated that there was no indirect effect of maternal antenatal depression on twelve month *vocd* score through six month CES-D score.

In terms of the group comparisons of maternal MLU scores, although groups were recruited based on their depression score during pregnancy, the results of this study are in keeping with what is reported in the current literature, that has previously reported no differences between depressed mothers in comparison with controls (Reissland et al., 2003; Cornish et al., 2008; Righetti-Veltema et al., 2002; Murray et al., 1993) as well as no differences between depressed and control mothers in comparison to mothers with a history of depression (Murray et al., 1993). This is despite significant differences between the Depressed group in comparison to the History and Control groups in both measures of depression, the HAM-D and CES-D, across all time-points of the study, as reported in Chapter 3. Indeed, Pound and colleagues (1988) reported no impact of depression for the amount of speech that mothers spoke to their infant but reported that rather it was the quality of speech that was associated by depression.

However in contrast to Pound et al.'s (1988) results, the current study found no group differences for maternal *vocd* scores, a measure of the quality of maternal linguistic input towards her child. This is perhaps unsurprising as maternal quality and quantity of language and child-directed speech is strongly associated with maternal education (Rowe, 2012) and the sample recruited for the current study had an overall high level of education with no differences in maternal education between the groups.

This current study is unique in examining the indirect effect of maternal depression during pregnancy through the association between maternal concurrent depression and maternal behaviour as reported with regards to maternal MLU scores at two and twelve months. As has previously been highlighted in this thesis, women with antenatal depression are at a high risk of continuation of symptoms into the postnatal period and of relapse of depression (Leigh & Milgrom, 2008). The results of this study further highlights the importance of identifying women with antenatal depression and supporting them to receive treatment during pregnancy, be it through pharmaceutical or psychological intervention. During pregnancy, women are in frequent contact with healthcare providers and medical professionals which allows for numerous opportunities to both screen and provide adequate therapeutic input to these women.

5.4.2 Maternal Vocal Responsiveness

Maternal vocal responsiveness was assessed at each postnatal time-point through two variables; response latency; measured by the duration of time it took for a mother to vocalise in response to the onset of vocal overture from her infant, and switching pause duration, measured by the duration of the elapsed time between the offset of an infant vocalisation and the onset of the mother's vocalisation. Although a mother's vocalisation was considered a response if it occurred within a five-second latency window from the onset of her infant's vocalisation, maternal vocal responses typically

occurred within two seconds of the onset of an infant vocalisation. There were no significant group differences for either response latency or switching pause duration between the Depressed, History or Control groups at any of the three postnatal time-points. Although this aspect of maternal behaviour has rarely been studied within the postnatal depression literature, these results are in contrast to previous reports that mothers with depression took longer to respond to their infants (Breznitz & Sherman, 1987; Bettes, 1988) and had longer switching pause durations (Zlochower & Cohn, 1996) in comparison with controls.

Although there were no reported differences between the Depressed History and Control groups for maternal response latency and switching pause duration, this study focused on only one modality of maternal response behaviour, that of vocal responsiveness. However, during interactions with their infants mothers use both facial affect and touch, in addition to vocalisation in order to respond to their infant's overtures for engagement. The use of differing modalities by mothers to respond to their infants was investigated by Keller et al (1999) who reported individual differences between mothers in terms of the modality through which they were most likely to respond to their infant. It was reported that mothers who reacted with high contingency towards their infant's non-vocal contingencies did not respond contingently to infant vocalisations and vice versa. Additionally, Van Egeren et al (2001) reported that some mothers responded with touch to infant vocalisations. It is therefore suggested that future research include differing modalities of initiation of interaction from both the infant and the mother. Including maternal touch as a response towards her infant is particularly important in samples with depressed mothers as it has previously been reported that mothers with depression provide very little touch to their infants and when touch is observed it is often functional and not affectionate (Feldman et al., 2004).

5.4.3 Maternal and Infant Matched Affect

Maternal and infant expression of affect was assessed within a mother-infant three minute free-play interaction at each time-point. Both mother and infant affect were coded according to specified behavioural signifiers of positive, neutral or negative affect. Due to the minimal proportion of time that any of the mothers displayed negative affect, a categorical variable, indicating whether mothers displayed any negative affect or not during each clip or not was also calculated. Mother-infant affective matching was calculated by measuring the proportion of time that infants and mothers were matched for either positive or neutral affect. A variable comprising total overall matched affect was calculated as a composite of these three scores.

For maternal affect, there were no significant group differences for the proportions of maternal positive, negative or neutral affect at two, six or twelve months. The number of mothers who displayed any negative affect did not differ between groups at two and six months. At twelve months, there was a higher prevalence of negative affect displayed by mothers in the Depressed group in comparison to mothers in the History and Control group. The current study also found no group differences for the proportion of maternal positive or neutral affect at any of the time-points. At two months, infants in the History group displayed a significantly higher proportion of positive affect in comparison to the infants in the Control group. There were no significant differences in the proportion of positive affect displayed for infants in the Depressed group in comparison to the History or Control group. There were no significant group differences for infant affect at six or twelve months. Lastly, the data in this study did not support the hypothesis that mother-infant dyads in the Depressed group would demonstrate less matched neutral, positive and overall affect in comparison to the History and Controls. In fact, dyads in the Control group at two months displayed the lowest proportions of matched positive and overall affect. For mother-infant dyads in the control group, the proportion of matched positive and

overall affect was significantly lower than that of the History group and there were no significant group differences between the Depressed group and either the History or Control groups. There were no significant group differences for matched affect at six or twelve months.

The data reported in this study do not support the hypothesis that mothers in the Depressed group would show less positive and neutral affect and less matched affect in comparison to the History group or Controls. Within the current literature, research predominantly focuses on mothers with postnatal depression and report conflicting results (e.g. Field et al. 1990; Beebe et al., 2008). To date, Goodman et al (2017) are the only authors to investigate the impact of antenatal depression on mother-infant affective matching, reporting an association between antenatal, but not postnatal depression, and lower affective matching in their mother-infant dyads. The results of the current study indicate that ability of a mother to match their infant's displays of affective behaviour is not related to antenatal depression. This is despite mothers in the Depressed group having significantly higher depressive symptoms at each time-point, as reported in Chapter 3, Section 3.4.4.

An unexpected finding was that mothers in the Control group matched positive and total affect for the lowest proportion of time at two months. This is perhaps explained by the significantly lower proportion of positive affect displayed by their infants at this time-point. However the results of this study are unable to address the causal nature or either the mother or infant's behaviour on each other due to only measuring affect that occurred at the same time. Mothers may follow the infant's lead and change her behaviour accordingly or the infant may follow the mother's behavioural cues (Feldman, 2003). Future studies investigating affective matching in mother-infant dyads should incorporate lead-lag analyses in order to address the question of whether it is the mother or the infant driving the behavioural change within the dyad (Feldman, 2003).

The finding that infants of non-depressed mothers display less positive and more negative affect during mother-infant interactions is not unique. A recent meta-analysis reported that infants of depressed mothers display more positive affect in the 'reunion' stage of the Still-Face Procedure (SFP) in comparison to controls (Graham et al., 2018). This paper suggests that this increased display of positive affect in the infants of depressed mothers during the SFP is a coping strategy used in order for the infant to regulate their own distress levels during this procedure (Graham et al., 2018). In addition, infant positive affect amplifies positive attachment signals in an attempt to engage maternal attention and support which would act as a buffer against further distress (Out et al., 2009; Weinberg & Tronick, 1996). However, it is difficult to make comparisons between studies employing the still-face procedure and the interactions recorded for the current study which were free-play interactions that were not designed to elicit maternal or infant distress. It is possible that some aspects of impairments in maternal interactive behaviour are subtle and difficult to detect unless the dyad is observed in a challenging or stressful context (Biringen et al., 2005). A possible suggestion for future studies of mother-infant interaction is the incorporation of a paradigm designed to elicit distress or challenge for the mothers or their infants, which may yield more information. Mother-infant interactions under these circumstances may be more powerful in detecting differences between depressed and non-depressed groups. However for research with clinical groups including a task of this nature may be too emotionally distressing for both mothers and their infants.

5.4.4 Methodological considerations for video recorded interactions

This study utilised a three minute video of a free-play interaction between mothers and infants recorded in their homes at each time-point. It is also important to consider that there may have been some methodological issues with regards to the manner in which the videos were recorded or coded which may have contributed to the findings in this

study. Recording within the home has advantages for higher ecological validity and more naturalistic assessment of the mother-infant relationship. However video recordings made outside of a laboratory setting means that it is difficult to maintain control of the environment and minimise distractions for the mother. An example of this are the potential competing demands that may arise from other children who may also be in the home. It is possible that the short duration of the three minute clips may have reduced the opportunity to capture variations in interaction quality over time (Biringen et al., 2005). However, other studies have successfully identified impairments in interactions in depressed mothers during observations of brief durations (Stein et al., 1991).

In this study, maternal responses were only coded in relation to infant non-distress vocalisations. Within the literature, mothers are reported to respond differently, and with a shorter latency to infant distress vocalisations. Furthermore Pearson et al (2011) previously used non-verbal responsive behaviours rather than verbal responsive behaviours as they are thought to reflect more instinctive and automatic responses that are less likely to be subject to social desirability. Lastly, at two months, the kappa value for maternal neutral affect was relatively low, indicating low agreement between coders. A potential reason for low agreement may have occurred as these clips were coded with one camera only, thus occasions would arise when the mothers face was obscured. At the later time-points of six and twelve months, it may have been clearer from other aspects of infant behaviour what the predominant display of affect was. However due to the limited behavioural repertoire in infants of two months, it is possible that this lack of clarity resulted in disagreements between coders. This may have contributed to more disagreement between coders regarding the nature of maternal affect in the video-recordings at this specific time-point.

5.4.5 Conclusions

Within this study, there were no reported group differences in interactive behaviour for mothers with a diagnosis of depression during pregnancy in comparison with mothers in the History or Control group. In fact, at two months, mothers and infants in the Control group demonstrated less positive and matched affect in comparison with the History group. Furthermore, there were no differences in measures of maternal linguistic input, measured by the mothers' mean length of utterance (MLU) and lexical diversity (*vocd*) or maternal responsiveness measured by maternal response latency to infant vocalisations and switching pause duration. Analyses of the sample as a whole revealed no significant associations between antenatal or postnatal measures of depression and response latency, switching pause duration or for positive and matched affect. However, there were significant associations between a number of the measures of maternal postnatal depression and maternal MLU and *vocd* scores. Further analyses using postnatal depression score as a mediator revealed an indirect effect of antenatal depression on maternal MLU at two and twelve months postpartum.

These results further highlight the importance of identifying and supporting women with antenatal depression to receive treatment and support. Future studies should incorporate additional measures of maternal responsiveness and lead-lag analysis into their designs and study maternal-infant interaction within more challenging, but emotionally safe, contexts for both the mother and her infant.

Chapter 6

Maternal-infant interactive behaviour and
infant neurodevelopment

6.1 Introduction

Antenatal depression is increasingly becoming recognised as a risk factor for a number of adverse outcomes during birth, the postnatal period and into later childhood and adulthood. However, the adverse effects of antenatal depression are more reliably reported in some domains of infant development in comparison to others. Antenatal depression has been consistently linked to a higher risk of obstetric complications and there is a strong association between depressive symptoms during pregnancy and an increased risk of emotional disorders in childhood and later adulthood (Grote et al., 2010; Kurki et al., 2000; Leis et al., 2014; Lahti et al., 2017). However, studies reporting on the links between antenatal depression and other aspects of infant outcome such as neurodevelopment report less reliable findings (Schechter et al., 2017; Hay et al., 2008; DiPietro et al., 2006). These discrepancies are possibly attributable to one major factor which is often overlooked within these studies; that of the postnatal environment and in particular the postnatal caregiving environment.

Infant neurodevelopment is one aspect of infant outcome that is particularly susceptible to environmental factors such as postnatal parenting quality (Stein et al., 2014). Given that within the first year mothers are frequently the primary caregiver of their infants, research studies investigating the influence of caregiving behaviour have predominantly focused on the mother-infant relationship. A wealth of literature has reported on the positive associations between maternal sensitivity and infant secure attachment in addition to social and cognitive development (Stams et al., 2002; De Wolff & van Ijzendoorn, 1997).

In recent years however, there has been increasing evidence to suggest that maternal interactive behaviour in the postnatal period can either ameliorate or exacerbate the effect of antenatal depression on infant outcomes. This provides tentative evidence for potential malleability in both infant behavioural and physiological systems (Van den Bergh et al., 2011). Maternal sensitivity has been

reported to moderate the relationship between antenatal stress and infant cognitive development (Schechter et al., 2017), maternal antenatal cortisol and infant cognitive development (Bergman et al., 2010) and maternal depression and infant cortisol reactivity (Kaplan et al., 2008; Feldman et al., 2009). In all of the above studies, better infant outcomes were reported when mothers demonstrated higher levels of sensitive behaviour. These studies provide early evidence for the malleability of the stress response system in early infant life and indicate that exposure to adverse conditions *in utero* may potentially be ameliorated in the context of a supportive postnatal environment. All of the above studies focus on the global construct of maternal sensitivity and there are no studies, to my knowledge, that have investigated the moderating role of more specific aspects of maternal behaviour such as maternal linguistic input, temporal contiguity or matched or positive affect on infant developmental outcomes.

6.1.1 Shared Mother-Infant Affective State and Infant Outcomes

Tronick and Gianino's (1986) *Mutual Regulation Model* posits that infants learn to regulate their biological, emotional and behavioural systems within the context of the mother-infant relationship. Within the first year, a key aspect of this develops in the context of the coordinative processes such as synchrony and affective behavioural matching that occur within mother-infant interactions (Feldman, 2007). A greater degree of time spent in 'matched' affect is typically an indicator of a good quality dyadic interaction (Moore et al., 2004; Lowe et al., 2012). In early infancy, maternal-infant affective matching serves to support early infant attachment and the development of the infant's self-regulation capacities (De Wolff & van Ijzendoorn, 1997). Later in infancy, synchronous interactions with caregivers facilitate early language acquisition through promoting opportunities within which infants can participate in the 'give and take' of social communication. Inter-subjectivity is associated with both receptive and

expressive infant language competencies (Bakeman & Adamson, 1984; Nicely et al., 1999; Lindsey et al., 2009).

The role that affective matching plays in facilitating emergent infant cognitive development is less clear. Kirsch et al (1995) investigated the impact of both maternal positive and matched positive affect on infant cognitive development and found that only positive affect was predictive of infant cognitive development. Maternal positive affect, in itself, has also been associated with higher verbal and performance IQ scores, an index of language and cognitive development ability respectively in infants of 18 months and later childhood (Pearson et al., 2011; Sheinkopf et al., 2016). Sheinkopf and colleagues (2016) propose that positive affect rather than matched affect, which can include shared neutral affective expression, is specific to facilitating emerging infant cognition. It is proposed that maternal positive expression increases the infant's motivation to engage with their mother, resulting in more opportunities for learning experiences within dyadic interactions.

6.1.2 Maternal Linguistic Input and Infant Outcomes

Maternal speech or infant-directed speech (IDS) is a fundamental element of mother-infant interactions. Maternal speech both engages and guides the infant's attention and functions to support the infant's developing self-regulatory capacities while also encouraging the infant's engagement with their environment. The core elements of the construct of maternal sensitivity apply directly to IDS and maternal linguistic input must be contingent to infant behaviour, appropriate to the infants developmental level and occur within a timeframe of response perceivable by the infant in order to facilitate infant linguistic and cognitive development (Tamis-LeMonda & Bornstein, 2002). Research is typically concerned with either the *quality* or *quantity* of maternal IDS and to what degree elements of either one or both are related to infant and child language outcomes. The *quantity* of maternal linguistic input is typically measured by recording

the frequency of words or utterances spoken by a mother towards her infant during an interaction (Rowe, 2012). On the other hand, the *quality* of speech is typically assessed through the degree of lexical or syntactical diversity that characterises a mother's IDS. Lexical diversity, which is typically measured through quantifying the number of unique or new words that a mother uses in reference to the total number of words used while speaking with her infant while syntactical complexity is denoted by calculating a mother's mean length of utterance (MLU): the average number of morphemes per utterance of the mother during a sample of speech (Rowe, 2012).

There is some debate within the literature as to whether the quality or the quantity of maternal linguistic input has the greatest impact on infant language outcomes. Some reports outline that lexical diversity is reported to be a better predictor of child language development than the quantity of words spoken (Pan et al., 2005; Ramirez-Esparza et al., 2014; Campisi et al., 2009). However, there are also studies that report how the quantity of speech that infants are exposed to is of equal importance (Huttenlocher et al., 1991; Hurtado et al., 2008; Adams et al., 2017; Weisleder & Fernald, 2013) with lower frequencies of maternal vocalisations reported to be predictive of later infant and childhood psychopathology such as ADHD, oppositional defiant disorder and other conduct disorders (Allely et al., 2013). Maternal linguistic input has also been associated with better cognitive outcomes for infants, particularly the aspects of maternal speech that incorporates the labelling of objects and actions as well as verbal encouragement and scaffolding (Landry et al., 2001).

An important factor to further consider regarding maternal speech is the duration of time or response latency, that a mother takes to respond to her infant's overtures to communicate, an element which is also considered in Ainsworth's definition of maternal sensitivity (Ainsworth et al., 1974). Within the first year, temporal contiguity plays a role in early infant language through encouraging infant vocalisations and influencing their phonology (Goldstein, King & West, 2003; Goldstein & Schwade, 2008). The element of turn-taking that occurs within mother-infant interactions is also

important for reinforcing the social-communicative functions of language (Tamis-LeMonda & Bornstein, 2002). During conversational exchanges two variables are often of interest. The first is the 'Switching-Pause' duration, the silence after an infant stops vocalising and the mother begins vocalising. The second is maternal response latency to infant overtures, measured by the duration of time between the onset or offset of an infant behaviour and the corresponding onset of a mother's behaviour.

There is no consensus as to what the 'ideal' latency window is within an interaction for response latency to infant communicative overtures or for switching pause duration. However, maternal response latencies vary depending on the communicative modality used and the function that the mother's behaviour aims to serve (Keller et al., 1999). Maternal response latency windows tend to be shortest for vocalisation to vocalisation responses and in responding to infant non-distress vocalisations it has been reported that mothers of three to four month olds tend to respond within one second (Van Egeren et al., 2001; Keller et al., 1999; Mastaka et al., 1993). Additionally, Ramey & Ourth (1971) reported that infants of three, six and twelve months of age only increased their rate of vocalisation when mothers responded immediately, demonstrating no vocalisation increases when their mothers delayed their response to either three or six seconds. During vocal exchanges, pauses or responses exceeding three seconds may signal a period of disengagement (Stern & Gibbon, 1979). However to allow for potential variability in response latencies, most research with infants allows for a latency window of five seconds. This latency window is based on evidence from temporal patterns in adults but it is hypothesised that briefer durations are required for infants to integrate words and experiences (Tamis-LeMonda & Bornstein, 2002).

6.1.3 Moderating effect of maternal interactive behaviour on infant developmental outcomes

Across the past decade, there has been accumulating evidence to support the moderating role that early life care plays in the relationship between antenatal or early life exposure to maternal depression and infant neurodevelopmental outcomes. Maternal sensitivity predicted better expressive language outcomes in infants of mothers with depression, whereas maternal intrusive behaviour has been reported to contribute to less optimal executive function (Gueron-Sela et al., 2018). There is emerging evidence to suggest that the programming effects of the intrauterine environment may also be modifiable through early postnatal experiences. This 'reversal' of fetal programming was first observed in animal models in the seminal studies completed by Weaver and colleagues (2004). These studies demonstrated that the effects of prenatal stress on offspring stress-reactivity was reversed when rat-pups were placed with high-care mothers. In one of the first studies to attempt to replicate this effect in humans, Sharp et al (2012) reported that higher maternal depression scores during pregnancy were associated with increased infant negative emotionality only when mothers reported low frequency of stroking their infant's face, back, stomach, arms and legs.

Sensitive maternal care in the postnatal period has also been reported to buffer the impact of antenatal stress on infant neurodevelopmental outcomes. Bergman et al (2010) reported a negative association between antenatal cortisol and cognitive development only in those children with an insecure attachment with their mother and not in infants with secure attachment. Moreover Schechter et al (2017) reported that maternal antenatal distress predicted lower cognitive ability and that this relationship was strongest for children whose mothers exhibited low levels of positive engagement. The results of these studies highlight the importance of early intervention for infants of mothers who may be at a higher risk of developmental delay as a result of maternal antenatal depression. However, more replication is needed, particularly in

order to understand the specific maternal behaviours which may be involved in this process. A greater understanding of the processes involved in the outcomes for both mothers and infants will allow for the development of more targeted and effective interventions in future research.

6.1.4 Study Outline

The primary aim of this study was to examine the relationship between maternal interactive behaviour and infant neurodevelopmental outcome at two, six and twelve months. At two months infant neurobehavioral development was measured using the Brazelton Neonatal Behavioural Assessment Scale (NBAS) and at six and twelve months the Bayley Scale of Infant Development (BSID) were used to assess infant cognitive, language and motor development. At all three time-points mothers also completed the social-emotional and adaptive behaviour questionnaires of the BSID. A short interaction between each mother and infant was recorded at each time-point. Each video clip was coded for maternal and infant positive, neutral or negative affect. Maternal vocal responses to infant vocalisations were also coded and maternal mean response latency and switching pause duration was calculated from each recording. All clips were transcribed and maternal mean length of utterance (MLU) and lexical diversity (*vocd*) were calculated from each transcript.

A secondary aim of this study was to determine whether maternal interactive behaviour moderated the relationships between maternal antenatal cortisol and infant outcome that have previously been reported in this thesis. Chapter four addressed the relationship between five indices of maternal antenatal cortisol and infant neurodevelopment at two, six and twelve months. At six months the results indicated a significant negative correlation between antenatal evening cortisol and infant cognitive development. At twelve months there was a positive association between maternal cortisol awakening response (CAR) and infant motor development. This study investigated whether maternal interactive behaviour had a moderating effect on the

relationships that were reported in Chapter 4 between antenatal cortisol and infant neurodevelopment.

Hypotheses

- 1) Higher maternal mean length of utterance (MLU) and lexical diversity scores would be positively associated with infant neurodevelopment at two, six and twelve months
- 2) Shorter maternal mean response latency and switching pause durations would be positively associated with infant neurodevelopment at two, six and twelve months.
- 3) Higher proportions of maternal positive affect and matched positive, neutral and overall affect would be positively associated with infant neurodevelopment at two, six and twelve months.
- 4) The relationship between maternal antenatal evening cortisol and infant six month cognitive development would decrease as maternal MLU, lexical diversity, positive affect and matched positive, neutral and overall affect increase and as maternal mean response latency and switching pause duration decreases.
- 5) The relationship between maternal antenatal cortisol awakening response and infant twelve month motor development score would increase as maternal MLU, lexical diversity, positive affect and matched positive, neutral and overall affect increase and as maternal mean response latency and switching pause duration decreases.

6.2 Method

6.2.1. Participants

Participants were recruited from the Perinatal Psychiatry services and antenatal booking clinics within the National Maternity Hospital, the Coombe Women and Infants University Hospital and the Rotunda Hospital in Dublin. Participants in their second or third trimester who met the inclusion and exclusion criteria were clinically assessed by Dr. Chaitra Jairaj, a research registrar in Psychiatry. Participants were recruited into a depressed, history or control group. Demographic data for the whole sample is presented in Section 3.4.2 of Chapter 3.

6.2.2 Measures

Maternal Demographic Characteristics

Maternal demographic information was recorded at the time of recruitment interview and included the following variables: maternal age, ethnicity, education, employment status and marital status.

Maternal health behaviours and obstetric factors

Maternal medication and current levels of cigarette and alcohol consumption were recorded. Details pertaining to the mother's obstetric history and current pregnancy were also recorded. These variables included: gravidity, parity, and previous obstetric complications.

Maternal Clinical Measures

The MINI International Neuropsychiatric Interview (M.I.N.I.) (Sheehan et al., 1998) and the Hamilton Rating Scale for Depression (HAM-D) (Hamilton, 1960) were completed by Dr. Chaitra Jairaj at recruitment. Mothers also completed the Center for Epidemiologic

Studies: Depression Scale (CES-D) (Radloff, 1977) and Perceived Stress Scale (PSS) (Cohen, Kamarck & Mermelstein, 1983) on recruitment to the study and at two, six and twelve months postpartum.

Infant Birth Characteristics

Infant birth details were obtained from participant medical records at each maternity hospital. In cases where these data were not available, the information was collected from the mother. Information on the mode of onset of labour, delivery method, infant gestational age at birth, weight at birth, one minute and five minute APGAR scores and head circumference were collected. Additional information on infant characteristics such as current weight, feeding method and hours of childcare per week were provided by the mother at the two, six and twelve month time-points.

Brazelton Neonatal Behavioural Assessment Scale-4th edition (NBAS) (Brazelton & Nugent, 2011).

The NBAS was carried out in a quiet, semi darkened room, with a temperature of 22-27°C in either the mother's house or in a room with the same conditions within TCIN where possible when the infant 7 weeks old. Mean infant age at assessment was 8 weeks, 1 day (Range: 7 weeks to 10 weeks 4 days). For analysis, data were grouped using the cluster-scoring method outlined by Lester, Als and Brazelton (1982) into seven domains: Habituation, Orientation, Motor, Range of State, Regulation of State, Autonomic Stability and Reflexes. In addition to these clusters, there are seven supplementary items which describe the infants overall performance over the course of the examination of which six were used: Quality of Alertness, Cost of Attention, Examiner Facilitation, General Irritability, Robustness and Endurance, State Regulation. NBAS data is available for 72 of the infants within this study.

Bayley Scales of Infant Development-3rd Edition (BSID-III) (Bayley, 2006)

Infants were assessed using the BSID-III at six and twelve months of age. The BSID consists of five administered subtests: cognitive, receptive language, expressive language, fine motor and gross motor. Raw scores are converted to scaled scores, which account for age, using the appropriate table in the manual of the BSID-III. Three composite scores; Cognitive, Language and Motor, are obtained from the scaled score of the cognitive subtest, the sum of the scaled scores for both the receptive and expressive language subtests and the sum of the fine and gross motor scaled scores respectively. At the six month time point, the mean age at testing was 6 months 13 days (Range: 5m 29 days to 7m 17 days). At the twelve month time point the mean age at testing was 12 months 19 days (Range: 12m 0 days to 14m 2 days).

Bayley-III Social-Emotional Scale (Greenspan, 2004)

The Bayley Social-Emotional (SE) was completed by the mother at the two, six and twelve month time points. All items are tallied and this comprises the SE raw score. This score is then converted to a scaled score and then to a composite score. The composite score for this measure is used for the purposes of the analysis.

Bayley-III Adaptive Behaviour Scales (Harrison & Oakland, 2003)

The Adaptive Behaviour Scales were completed by the mother at the two, six and twelve month time-points. The total score for each scale is tallied and converted to a General Adaptive Composite. The composite score for this measure is used for the purposes of the analysis.

6.2.3 Maternal Salivary Cortisol

Participants collected saliva samples at one point during their pregnancy using Salivette™ swabs (Sarstedt). Mothers were asked to collect their saliva samples at five points across one day at the following times: Upon waking (0 minutes) and then 30 minutes, 60 minutes, 12 hours (720 minutes) and 12.5 hours (750 minutes) after waking. Mothers returned the saliva samples to Trinity College by post. Mean gestational age at which cortisol was sampled was 26.4 (+/-3.85) weeks, range 18-34 weeks.

The specific cortisol indices used for this study included:

- (i) *AUC with respect to increase (AUCi)*: AUCi is a variable that captures the AUC with respect to increase from baseline and emphasises the change of cortisol over time.
- (ii) *PM average*: The average of the two evening cortisol values.

Log-transformed cortisol values were used to calculate the above parameters. The AUC with respect to increase (AUCi) was computed using formulae outlined by Fekedulegn and colleagues (2007).

6.2.4 Maternal-Infant Interaction

Video Recordings

Following the completion of the developmental assessment at each time point a three minute video clip of a free play interaction between each mother and her infant was recorded using a NIKON D3100, a 14.2-megapixel DX format DSLR camera. Each mother was instructed to 'Play or interact with your baby as you usually would. You can use toys or not as you choose'. Mothers were allowed to choose how they would position their baby and what toys they would use, if any.

Affect

The videos were coded for affect by three coders who were completely blind to the purpose of the study. All coding was completed using INTERACT™ software (Mangold, 2006). Clips were coded for both maternal and infant moment to moment affective behaviour in separate phases. For both mother and infant, affective behaviour was coded as either positive, neutral or negative using a coding system (Appendix x) which outlined behavioural signifiers for each classification of affective behaviour. This coding scheme was designed by the author along with Dr. Elizabeth Nixon and Dr. Jean Quigley of the School of Psychology, Trinity College. The proportion of time that mother and infant displayed either positive, neutral or negative affect was recorded as a percentage resulting in a possible six variables for each mother-infant dyad at two, six and twelve months. Four additional variables representing the proportion of time where mother and infant were matched for neutral, positive and negative affect and a composite variable comprising the total proportion of time that mothers and infants were matched for affect were also recorded. This variable was obtained through the co-occurrence function within INTERACT which searches for classes; situations where mother or infant are displaying positive, neutral or negative affect; that occur simultaneously for both mother and infant. INTERACT then calculates the total percentage of co-occurring events for each class separately. This comprises the variables of total matched neutral, negative or positive affect. These percentages were then added to create the percentage of time per clip that each dyad were matched for overall affect.

Maternal response latency and switching pause duration

The videos were coded for infant and maternal vocalisations by three coders who were completely blind to the purpose of the study. Coding for this variable was completed using INTERACT™ software (Mangold, 2006). In the first phase, any effortful or speech-like non-distress vocalisation made by the infant was coded. Infant sounds such as

crying, fussing, laughing or other vegetative sounds were not coded. In the next phase any maternal vocalisations uttered within five seconds of the onset of an infant vocalisation were coded. Maternal sounds such as laughing or noises such as kisses or 'blowing raspberries' were not coded. Vocalisations made outside of the five second window were designated as a non-contingent vocal response. Two variables were obtained from this data: Mean response latency duration (RL) and Switching Pause (SP) Duration. Mean maternal response latency for each participant was calculated by averaging the duration of time between the onset of the infant vocalisation and the onset of the mother's vocalisation. Switching pause duration was calculated by averaging the duration of time between the offset of an infant vocalisation and the onset of a maternal vocalisation for each participant. If the infant made no vocal overtures towards their mother during the three minute video-clip no data was coded for this clip. At two months there were no vocal overtures from eight of the infants [Depressed=1, History=3, Control=4], at six months there were no vocal overtures from two of the infants [Depressed=1, History=1] and furthermore at twelve months there were no vocal overtures from two of the infants [History=1, Control=1].

Maternal mean length of utterance (MLU) and lexical diversity (vofd)

All maternal vocalisations observed in the video clips were transcribed by the author using CLAN (MacWhinney, 2000). Preliminary checks using the *CHECK* and *MOR* utilities were completed to ensure that the transcripts were set up correctly and to ensure that words were transcribed in the correct morphological structure. Two variables were obtained from the transcripts using the *KIDVAL* utility within the CLAN program: mean length of utterance (MLU) and vocal diversity (vofd).

Maternal mean length of utterance (MLU) is a measure of maternal language complexity and is often used as a proxy measure of grammatical input (Sandbank & Yoder, 2016). MLU is denoted by the average number of morphemes per utterance of

the mother during a sample of speech. *D (vocd*; Richards & Malvern, 1997) is a measure of vocal diversity which is based on the entire sample of words produced by the mother within a sample of speech. It is advantageous over other measures of vocal diversity such as the Type-Token Ratio, calculated by dividing the total number of unique words used by the total of words spoken, as it allows comparisons of speech samples of varying sizes. Values for both MLU and *D (vocd)* were obtained from each transcript at two, six and twelve months.

Inter-Rater Reliability

Inter-rater reliability for the affect and vocalisation variables was completed by three research assistants who were completely blind to the purpose of the study. Inter-rater reliability was calculated for 16-26% of the video clips. Time-unit *Kappa* values reflecting the extent of agreement for positive, neutral and negative affect for both mother and infant are presented in Table Chapter 2, Table 2.5. Percentage agreement for the mother-infant vocalisations are also presented in Chapter 2, Table 2.5.

Interpretation of the value of *Kappa* is dependent on the number of categories that are coded. Within this study there were three potential categories in which affect was coded for both mother and infant; positive, neutral or negative, and whose frequencies were highly variable. Therefore kappa scores above; .83, .68, .55 represent observer reliability of 95%, 90% and 85% accuracy respectively (Bakeman and Quera, 2011).

Missing and Excluded Video Recordings

A number of mothers within this sample were not native English speakers and spoke to their infants in a language other than English. These clips were not transcribed and thus MLU or VOCD was not measured in these participants. In addition, a number of video clips are missing from the 2 month time-point for two reasons: (i) infants born in the

initial part of the study did not partake in the developmental assessments as this arm of the study had not commenced yet and (ii) a number of infants were asleep at the time of the video recording. The participants for which interaction data was available is presented in Chapter 2, Table 2.4.

6.2.5 Statistical Analyses

All data were analysed using SPSS (Version 24, IBM). All data were firstly assessed for normality using the Shapiro-Wilk test. Due to the presence of positive skewness in the variables measuring affect, these variables were transformed using the ARCSINE transformation (Cohen & Cohen, 1983). Raw cortisol data was not normally distributed and was therefore log transformed in order to allow for analysis using general linear models.

Non-parametric data was analysed using Spearman's *Rho* partial correlations. Spearman's correlations were completed with and without controlling for the covariates of maternal education, parity and maternal current CES-D score. However, due to missing data within the CES-D variable and the necessity for listwise deletion when conducting non-parametric partial correlation analysis, this resulted in $n=25$ cases being excluded from the analysis. As the results obtained from the partial correlation analysis provides a more conservative account of the data, these values for *rho* will be presented. However, the direction of all statistically significant Spearman's correlations were the same with or without the inclusion of covariates. Simple linear regression analysis was used to measure the associations between variables that were normally distributed. These initial analyses were conducted without controlling for confounding variables of maternal education, parity and current depression. However these confounding variables were included in the final multiple regression analyses.

Moderation analysis was conducted using Model 1 of PROCESS, an SPSS macro (Hayes, 2013). PROCESS uses a regression based model to test the combined effect of two variables, otherwise known as an interaction effect, on a third variable (Field, 2013). In PROCESS the interaction effect is calculated automatically by the software. Moderation analyses were used to determine whether maternal antenatal cortisol interacted with maternal postnatal interactive behaviour to predict infant cognitive or motor development scores. Each model included either cognitive or motor development as the outcome variable, antenatal cortisol variable as the independent

variable and maternal interactive behaviour as the moderator. To interpret the model, simple slopes analysis was used. Simple slopes analysis considers the conditional indirect effect with the estimation for three points of the moderator: at the mean, one standard deviation above and one standard deviation below the mean. Within the models assessing the combined influence of maternal antenatal evening cortisol and maternal interactive behaviour on infant cognitive development at six months, maternal six month CES-D score was used as a covariate. Due to missing values for the cortisol awakening response variable (AUCi) sample size was greatly reduced (n=46). As a result, current maternal depression was not used as a covariate in the models analysing the combined influence of maternal cortisol awakening response and maternal interactive behaviour and infant motor development at twelve months as there was not sufficient power to accommodate more than three predictor variables in the model at once.

Maternal Education and parity were chosen as covariates for the data analysis. Parity was chosen as a covariate as a larger family size has been reported to reduce the quality and quantity of parent-infant interactions (Steelman et al., 2002). Maternal education was also chosen as a covariate as early maternal dialogue with her infant has been shown as a function of the mother's educational level (Rowe, 2012). Both maternal education and parity are also known to be independent predictors of infant neurodevelopmental outcome (Jedrychowski et al., 2009).

6.3 Results

6.3.1 Maternal Interactive Behaviour and Infant Neurodevelopment at Two Months

Relationship between maternal MLU, vocd and infant NBAS clusters, NBAS supplementary items and the Social-Emotional (SE) and Adaptive Behaviour (AB) scales of the BSID

At two months Spearman's ρ partial correlations, controlling for maternal education, parity and two month CES-D score, were conducted to determine the relationship between maternal two month MLU and the five clusters of the NBAS and the six supplementary items. There was a significant positive correlation between maternal two month MLU and the *Orientation* cluster of the NBAS ($\rho=.339$, $p=.040$). There were no statistically significant correlations between two month MLU and the remaining NBAS clusters or any of the supplementary items. Simple linear regression analyses conducted to assess the relationship between maternal MLU at two months and infant scores on the two month SE and AB scales of the BSID were not statistically significant. Regression coefficients are presented in Table 6.3

Spearman's ρ partial correlations indicated no statistically significant correlations between maternal *vocd* at two months and any of the clusters of the NBAS or the supplementary items. Simple linear regression analyses conducted to assess the relationship between maternal *vocd* score at two months and infant scores on the two month SE and AB scales of the BSID were not statistically significant. Regression coefficients are presented in Table 6.3

Relationship between maternal mean response latency (RL), mean switching pause (SP) duration and the infant NBAS clusters, NBAS supplementary items and the Social-Emotional and Adaptive Behaviour scales of the BSID

At two months Spearman's ρ partial correlations, controlling for maternal education, parity and two month CES-D score were conducted to assess the relationship between maternal two month RL and the five clusters of the NBAS and the six supplementary items. None of these correlations were statistically significant. Simple linear regression analyses conducted to assess the relationship between maternal RL at two months and infant scores on the two month SE and AB scales of the BSID were also not statistically significant. Regression coefficients are presented in Table 6.3

Spearman's ρ partial correlations indicated no statistically significant associations between maternal SP at two months and any of the clusters of the NBAS, the NBAS supplementary items, the SE scale or the AB scale of the BSID.

Relationship between maternal positive affect and the infant NBAS clusters, NBAS supplementary items and the Social-Emotional and Adaptive Behaviour scales of the BSID

At two months Spearman's ρ partial correlations, controlling for maternal education, parity and two month CES-D score were conducted to assess the relationship between maternal positive affect and infant scores on the NBAS clusters (Table 6.1) and supplementary items (Table 6.2). There was a statistically significant negative correlation between maternal positive affect and the *Range of State* item of the NBAS clusters ($\rho = -.426$, $p = .003$). There were no other significant correlations between maternal positive affect and the remaining NBAS clusters. There were also statistically significant correlations between maternal positive affect and *Quality of Alertness* ($\rho = .439$, $p = .006$), *Cost of Attention* ($\rho = .492$, $p = .002$), *Examiner Facilitation*

($\rho=.388$, $p=.016$), *General Irritability* ($\rho=.448$, $p=.005$) and *Robustness and Endurance* ($\rho=.550$, $p<.000$) items.

Simple linear regression analyses conducted to assess the relationship between maternal positive affect and infant scores on the two month Social-Emotional (SE) and Adaptive Behaviour (AB) scales of the BSID were not statistically significant. Regression coefficients are presented in Table 6.3

Relationship between maternal-infant matched positive, matched neutral and total matched affect and the infant NBAS clusters, NBAS supplementary items and the Social-Emotional and Adaptive Behaviour scales of the BSID

At two months Spearman's ρ partial correlations, controlling for maternal education, parity and two month CES-D score were conducted to assess the relationship between maternal matched positive affect, matched neutral affect and total matched affect and infant scores on the NBAS clusters (Table 6.1) and supplementary items (Table 6.2). There were statistically significant correlations between matched neutral affect and infant *Range of State* ($\rho=.324$, $p=.027$) and matched positive affect and *Range of State* ($\rho=-.440$, $p=.002$). There were no other statistically significant correlations between matched positive, neutral and total affect and the remaining NBAS clusters.

There were statistically significant correlations between matched neutral affect and the *Quality of Alertness* ($\rho=-.398$, $p=.013$), *Cost of Attention* ($\rho=-.391$, $p=.015$), *Examiner Facilitation* ($\rho=-.331$, $p=.042$) and the *Robustness and Endurance* ($\rho=-.486$, $p=.002$) items and between matched positive affect and the *Cost of Attention* ($\rho=.315$, $p=.038$) and *Robustness and Endurance* ($\rho=.325$, $p=.031$) items of the NBAS. There were no statistically significant correlations between any of the NBAS clusters or supplementary items and total matched affect.

Simple linear regression analyses conducted to assess the relationship between maternal-infant matched positive, neutral and total affect and infant scores on the two month SE and AB scales of the BSID were not statistically significant. Regression coefficients are presented in Table 6.3

Table 6.1: Associations between maternal positive affect, maternal-infant matched positive, neutral and total matched affect and the clusters of the NBAS at two months.

	1	2	3	4	5	6	7	8	10
1 Positive Affect	-								
2 Matched Neutral	.818***	-							
3 Matched Positive	.731***	-.507***	-						
4 Total Matched	-.115	.380**	.411**	-					
5 Orientation	.168	-.157	-.066	-.270	-				
6 Motor	.132	-.143	-.007	-.185	.348	-			
7 Range of State	-.426**	.324*	-.440**	-.109	-.103	.040	-		
8 Regulation of State	.162	-.202	-.038	-.174	.170	.277	-.256	-	
10 Autonomic	.042	-.128	-.089	-.112	.092	.111	-.165	.210	-

*p<.05, **p<.01, ***p<.001

Table 6.2: Associations between maternal positive affect, matched positive, neutral and total matched affect and the supplementary items of the NBAS at two months.

	1	2	3	4	5	6	7	8	9	10
1 Positive Affect	-									
2 Matched Neutral	.820***	-								
3 Matched Positive	.724***	-.514**	-							
4 Total Matched	-.175	.451**	.362*	-						
5 Quality of Alertness	.439**	-.398*	.225	-.275	-					
6 Cost of Attention	.492**	-.391*	.359*	-.081	.671***	-				
7 Examiner Facilitation	.388*	-.331*	.158	-.199	.711***	.868***	-			
8 General Irritability	.448**	-.251	.304	-.065	.598***	.780***	.689***	-		
9 Robustness & Endurance	.550***	-.486**	.432**	-.176	.605***	.646***	.644***	.574***	-	
10 State Regulation	.306	-.301	.203	-.131	.739***	.766***	.731***	.706***	.614***	-

*p<.05, **p<.01, ***p<.001

Table 6.3: Regression coefficients for the associations between the maternal interactive behaviour variables and the Social-Emotional and Adaptive behaviour scales of the BSID at two months.

Variable	Social-Emotional			Adaptive Behaviour		
	B	SE	beta	B	SE	beta
MLU	-2.427	1.790	-.192	-2.236	1.850	-.175
<i>vocd</i>	.031	.180	.025	.125	.185	.101
Response Latency	-.004	.004	-.132	.003	.004	.092
Positive Affect	8.716	5.938	.185	6.726	6.131	.141
Matched Positive	4.613	5.748	.102	-.888	5.923	-.020
Matched Neutral	-7.609	6.479	-.149	-8.945	6.615	-.173
Total Matched	-.036	.081	-.058	-.108	.082	-.169

6.4.2 Maternal Interactive Behaviour and Neurodevelopment at Six months

Relationship between maternal MLU, vocd and the infant cognitive, language, motor, social-emotional and adaptive behaviour scales of the BSID

Simple linear regression analyses were conducted to assess the associations between maternal MLU and six month scores on the cognitive, language and motor, social-emotional and adaptive behaviour scales of the BSID. None of the regression analyses were statistically significant. Regression coefficients are presented in Table 6.4.

Simple linear regression analyses were conducted to assess the associations between maternal *vocd* and six month scores on the cognitive, language and motor, social-emotional and adaptive behaviour scales of the BSID. Regression coefficients are presented in Table 6.5. There was a significant negative association between maternal *vocd* score and the cognitive scale of the BSID at six months [$F(1, 64) = 7.639, p = .007, \beta = -.327$]. A subsequent multiple regression which included the covariates of maternal education, parity and current maternal depressive symptoms was statistically significant [$F(4, 50) = 3.034, p = .026$] accounting for 19.5% of the variance with *vocd* as the only statistically significant predictor of six month cognitive development ($\beta = -.321, p = .017$).

There were no statistically significant associations between maternal six month *vocd* and the language, motor, SE or AB scales of the BSID. Regression coefficients are presented in Table 6.4 and Table 6.5.

Relationship between maternal mean response latency (RL) and mean switching pause duration (SP) and infant cognitive, language, motor, social-emotional and adaptive behaviour scales of the BSID

Simple linear regression analyses were conducted to assess the associations between maternal RL and the cognitive, language, motor, social-emotional and adaptive behaviour scales of the BSID at six months. There was a statistically significant positive association between maternal RL and infant language development [$F(1, 80) = 4.528$, $p = .036$, $\beta = .231$]. A subsequent multiple regression which included the covariates of maternal education, parity and current maternal depressive symptoms was not statistically significant [$F(4, 64) = 2.294$, $p = .069$]. None of the remaining regression analyses were statistically significant. Regression coefficients are presented in Table 6.4 and Table 6.5.

Spearman's ρ partial correlations, controlling for maternal education, parity and six month CES-D score were conducted to assess the relationship between SP duration and the infant scales of the BSID. None of the Spearman's correlations were statistically significant.

Relationship between maternal positive affect and the infant cognitive, language, motor, social-emotional and adaptive behaviour scales of the BSID

Simple linear regression analyses were conducted to assess the associations between maternal positive affect and the infant cognitive, language, motor, social-emotional and adaptive behaviour scales of the BSID. None of the regression analyses were statistically significant. Regression coefficients are presented in Table 6.4 and Table 6.5.

Relationship between maternal-infant matched positive, neutral and total matched affect and the infant cognitive, language, motor, social-emotional and adaptive behaviour scales of the BSID

Simple linear regression analyses were conducted to assess the associations between maternal-infant matched neutral, positive and total affect and infant scores on the cognitive, language, motor, social-emotional and adaptive behaviour scale of the BSID. None of the regression analyses were statistically significant. Regression coefficients are presented in Table 6.4 and Table 6.5.

Table 6.4: Unadjusted regression coefficients for the associations between the maternal interactive behaviour variables and the cognitive, language and motor scales of the BSID at six months.

Variable	Cognitive			Language			Motor		
	B	SE	beta	B	SE	beta	B	SE	beta
MLU	-.223	.957	-.028	1.067	1.104	.118	1.569	1.296	.146
<i>vocd</i>	-.231	.083	-.327**	.069	.102	.086	-.184	.119	-.192
Response Latency	-.001	.001	-.073	.003	.001	.231*	.000	.002	-.026
Positive Affect	1.382	3.540	.043	.601	4.102	.016	-.955	4.869	-.022
Matched Positive	-.627	3.865	-.018	-2.919	4.465	-.072	-6.498	5.266	-.135
Matched Neutral	-.516	3.909	-.014	1.336	4.525	.033	.645	5.374	.013
Total Matched	-.021	.068	-.035	-.105	.077	-.149	-.112	.092	-.134

*p<.05, **p<.01

Table 6.5: Regression coefficients for the associations between the maternal interactive behaviour variables and the Social-Emotional and Adaptive behaviour scales of the BSID at six months.

Variable	Social-Emotional			Adaptive Behaviour		
	B	SE	beta	B	SE	beta
MLU	-.3234	2.055	-.206	-1.199	1.669	-.095
<i>vocd</i>	-.133	.192	-.094	-.102	.154	-.090
Response Latency	.000	.003	.014	-.001	.002	-.067
Positive Affect	3.603	7.826	.056	1.538	6.222	.030
Matched Positive	-3.678	8.542	-.052	3.527	6.779	.062
Matched Neutral	-3.016	8.643	-.042	-1.118	6.868	-.019
Total Matched	-.192	.148	-.157	.063	.119	.064

6.4.3 Maternal Interactive Behaviour and Neurodevelopment at Twelve Months

Relationship between maternal MLU, vocd and the infant cognitive, language, motor, social-emotional and adaptive behaviour scales of the BSID

Simple linear regression analyses were conducted to assess the associations between twelve month maternal MLU and infant scores on the cognitive, language, motor, social-emotional and adaptive behaviour scales of the BSID. There was a statistically significant positive association between maternal MLU and motor development at twelve months [$F(1, 64) = 8.001, p = .006, \beta = .333$]. A subsequent multiple regression which included the covariates of maternal education, parity and current maternal depressive symptoms was statistically significant [$F(4, 57) = 2.934, p = .028$] accounting for 17.1% of the variance with MLU as the only statistically significant predictor of twelve month motor development ($\beta = .402, p = .005$).

None of the remaining regression analyses were statistically significant. Regression coefficients are presented in Table 6.7.

Simple linear regression analyses were conducted to assess the associations between twelve month maternal *vocd* and scores on the cognitive, language, motor, social-emotional and adaptive behaviour scales of the BSID. None of the regression analyses were statistically significant. Regression coefficients are presented in Table 6.7.

Relationship between maternal mean response latency (RL) and mean switching pause duration (SP) and infant cognitive, language, motor, social-emotional and adaptive behaviour scales of the BSID

Simple linear regression analyses were conducted to assess the associations between maternal RL and infant scores on the cognitive, language, motor, social-emotional and adaptive behaviour scales of the BSID at twelve months. None of the regression

analyses were statistically significant. Regression coefficients are presented in Table 6.6 and Table 6.7.

Spearman's *rho*, partial correlations, controlling for maternal education, parity and twelve month CESD score were conducted to assess the relationship between SP duration and the infant scales of the BSID. None of the Spearman's correlations were statistically significant.

Relationship between maternal positive affect and the infant cognitive, language, motor, social-emotional and adaptive behaviour scales of the BSID

Simple linear regression analyses were conducted to assess the associations between twelve month maternal positive affect and infant scores on the cognitive, language, motor, social-emotional and adaptive behaviour scales of the BSID at twelve months. There was a statistically significant positive association between maternal positive affect and infant language development at twelve months [$F(1, 74) = 8.565, p = .005, \beta = .322$]. A subsequent multiple regression which included the covariates of maternal education, parity and current maternal depressive symptoms was statistically significant [$F(4, 65) = 3.151, p = .02$] accounting for 16.2% of the variance with positive affect as the only statistically significant predictor of twelve month language development ($\beta = .311, p = .009$).

None of the remaining regression analyses were statistically significant. Regression coefficients are presented in Table 6.6 and 6.7

Relationship between maternal-infant matched positive, neutral and total matched affect and the infant cognitive, language, motor, social-emotional and adaptive behaviour scales of the BSID

Simple linear regression analyses were conducted to assess the associations between twelve month maternal matched neutral, positive and total affect and scores on the cognitive, language, motor, social-emotional and adaptive behaviour scales of the BSID at twelve months. There was a statistically significant negative association between matched neutral affect and the language scale of the BSID at twelve months [$F(1, 74) = 4.859$, $p = .031$, $\beta = -.248$]. A subsequent multiple regression which included the covariates of maternal education, parity and current maternal depressive symptoms was not statistically significant [$F(4, 65) = 2.201$, $p = .079$]. None of the remaining regression models were statistically significant. Regression coefficients are presented in Table 6.6 and 6.7

Table 6.6: Unadjusted Regression coefficients for the associations between the maternal interactive behaviour variables and the cognitive, language and motor scales of the BSID at twelve months.

Variable	Cognitive			Language			Motor		
	B	SE	beta	B	SE	beta	B	SE	beta
MLU	1.913	1.186	.195	2.144	1.154	.231	2.740	.969	.333**
<i>vocd</i>	.207	.118	.214	.029	.119	.032	.090	.102	.111
Response Latency	-.001	.002	-.075	-.001	.002	-.055	.000	.002	.031
Positive Affect	9.759	5.871	.181	16.423	5.611	.322**	7.352	4.991	.162
Matched Positive	1.979	5.870	.037	5.189	5.801	.103	2.630	4.969	.059
Matched Neutral	-11.433	6.456	-.192	-13.948	6.328	-.248*	-9.176	5.479	-.184
Total Matched	-.089	.091	-.108	-.097	.090	-.125	-.082	.077	-.119

*p<.05, **p<.01

Table 6.7: Regression coefficients for the associations between the maternal interactive behaviour variables and the Social-Emotional and Adaptive behaviour scales of the BSID at twelve months.

Variable	Social-Emotional			Adaptive Behaviour		
	B	SE	beta	B	SE	beta
MLU	1.037	1.870	.071	1.367	1.183	.153
<i>vocd</i>	-.037	.188	-.026	.061	.120	.069
Response Latency	8.732 E-5	.003	.003	.002	.002	.133
Positive Affect	3.332	9.359	.041	.156	5.935	.003
Matched Affect	11.256	9.124	.142	2.058	5.835	.042
Matched Neutral	-2.301	10.320	-.026	-.775	6.539	-.014
Total Matched	.113	.143	.091	.000	.091	.001

6.4.4 Associations between maternal antenatal cortisol and infant neurodevelopment.

As reported in Chapter Four, there were statistically significant correlations between two of the maternal antenatal cortisol indices and infant neurodevelopmental outcome at six and twelve months. To recap, there was a statistically significant negative correlation between maternal evening cortisol (PM avg) and cognitive development at six months ($r=-.298, p=.008$) and a statistically significant positive correlation between maternal antenatal cortisol awakening response (AUCi) and infant motor development at twelve months ($r=.327, p=.011$).

Further analyses were undertaken on the sample in order to determine whether there was an association between the combined effect or interaction of antenatal cortisol and maternal interactive behaviour on infant neurodevelopmental outcome.

6.4.5 The interaction of maternal antenatal evening cortisol and maternal interactive behaviour on infant cognitive development at six months.

Moderation analyses, using PROCESS, were conducted to determine if there was an interaction effect of maternal evening cortisol and each of the seven maternal interactive variables on infant cognitive development at six months. Current maternal depression, measured using six month CESD score was used as a covariate in each model.

The model investigating the combined influence of maternal antenatal evening cortisol and maternal total matched affect on six month cognitive development was statistically significant [$F(4, 60)=3.390, p=.015$] explaining 18.43% of the variance. Further investigations on the interaction effect were completed using simple slopes analysis and the relationship between antenatal evening cortisol and six month cognitive development was tested at three levels of total matched affect, one standard deviation

(SD) above the mean, at the mean and one SD below the mean. Antenatal evening cortisol significantly predicted cognitive development when total matched affect was one SD below the mean [$B=-19.90$, $p=.002$] but not when total matched affect was at the mean [$B=-8.823$, $p=.05$] or one SD above the mean [$B=2.347$, $p=.733$]. These results indicate that there is a significant negative relationship between antenatal evening cortisol and cognitive development at six months when total matched affect is one SD below the mean (Figure 6.1).

None of the remaining moderation analyses were statistically significant. Regression coefficients are presented in Table 6.8

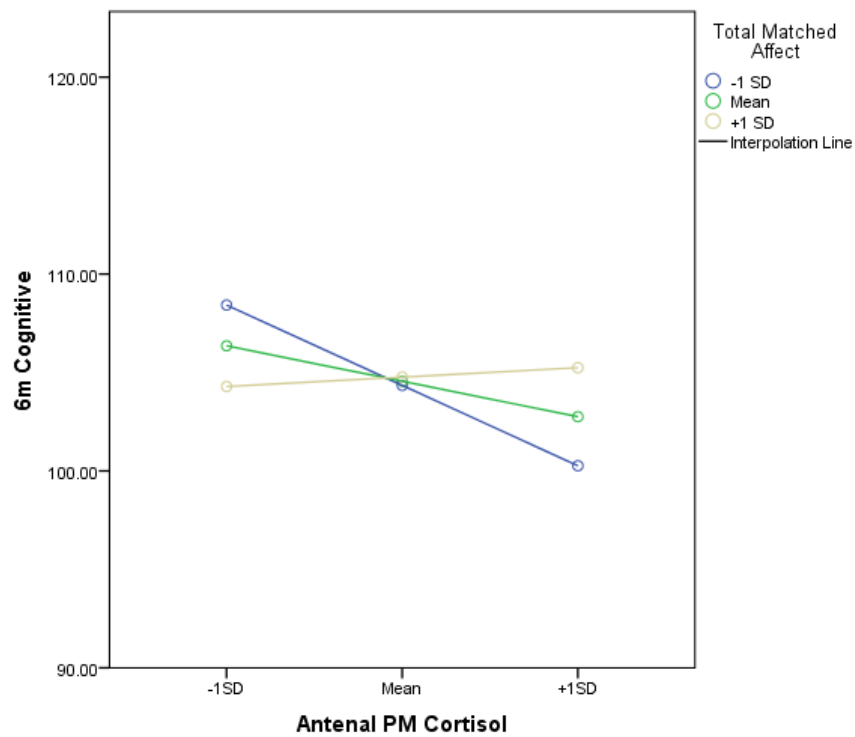


Figure 6.1: Simple slopes equations of the regression of antenatal cortisol on six month cognitive development at three levels of total matched affect.

Table 6.8: *B* coefficients pertaining to the interaction terms considered in each regression model and infant cognitive development at six months.

Outcome Variable: 6m Cog	b	CI	SE	t	p
<i>Interaction</i>					
Pm Avg x MLU	-2.43	-12.579, 7.708	5.045	-.483	.632
Pm Avg x vocd	-.118	-.286, .050	.084	-1.411	.165
Pm Avg x Response Latency	-.000	-.003, .002	.006	-.172	.864
Pm Avg x Positive Affect	-5.022	-43.465, 33.421	19.225	-.261	.795
Pm Avg x Matched Positive	6.309	-37.656, 50.274	21.986	.287	.775
Pm Avg x Matched Neutral	18.922	-23.077, 60.921	21.003	.901	.371
Pm Avg x Total Matched	.817	.123, 1.511	.347	2.356	.022

6.4.6 The combined influence of maternal cortisol awakening response and maternal interactive behaviour and infant motor development at twelve months.

Moderation analyses, using PROCESS, were conducted to determine if there was a combined effect of maternal CAR and each of the seven maternal interactive variables on infant motor development at twelve months. Due to missing values for the cortisol awakening response variable (AUCi) sample size was greatly reduced ($n=46$). As a result, current maternal depression was not used as a covariate in the model as there was not sufficient power to accommodate more than three predictor variables in the model at once.

The model investigating the combined influence of maternal antenatal cortisol awakening response and maternal lexical diversity on twelve month motor development was statistically significant [$F(3, 43)=3.419, p=.026$] explaining 19.63% of the variance. Further investigations on the interaction effect were completed using simple slopes analysis and the relationship between antenatal CAR and twelve month motor development was tested at three levels of lexical diversity (*vocd*), one standard deviation (SD) above the mean, at the mean and one SD below the mean. Antenatal CAR significantly predicted motor development when lexical complexity was at the mean [$B=.019, p=.008$] and one SD above the mean [$B=.036, p=.003$] but not when *vocd* was one SD below the mean [$B=.002, p=.779$]. These results indicate that there is a significant positive relationship between antenatal CAR and motor development at twelve months at average and above levels of maternal lexical diversity (Figure 6.2).

None of the remaining moderation analyses were statistically significant. Regression coefficients are presented in Table 6.9

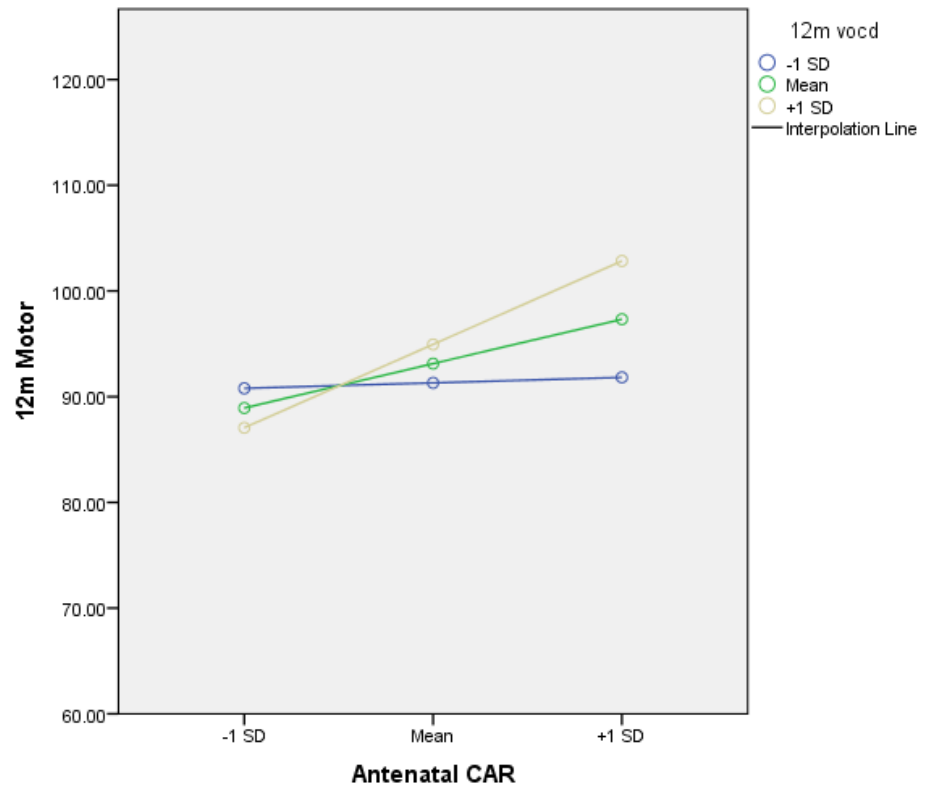


Figure 6.2: Simple slopes equations of the regression of antenatal CAR on twelve month motor development at three levels of lexical complexity.

Table 6.9: *B* coefficients pertaining to the interaction terms considered in each regression model and infant motor development at twelve months.

12m Motor development	b	CI	SE	t	p
AUCi x MLU	.001	-.012, .013	.006	.184	.855
AUCi x <i>vocd</i>	.001	.000, .003	.001	2.362	.023
AUCi x Response Latency	.000	.000, .000	.000	.373	.718
AUCi x Positive Affect	-.010	-.050, .030	.020	-.506	.615
AUCi x Matched Positive	.004	-.048, .056	.026	.155	.877
AUCi x Matched Neutral	.008	-.038, .054	.023	.355	.724
AUCi x Total Matched	.001	-.000, .001	.000	1.252	.216

6.4 Discussion

The primary aim of this study was to assess the relationship between maternal interactive behaviour and infant neurodevelopmental outcome at two months using the NBAS and at six and twelve months using the BSID. A short interaction between each mother and infant was recorded at each time-point and was coded for maternal and infant positive, neutral or negative affect as well as infant vocalisations and maternal vocal responses. In addition, values for maternal MLU and *vocd* were obtained from the transcript for each interaction. The second aim of this study was to determine whether maternal interactive behaviour moderated the relationship between antenatal maternal cortisol and infant neurodevelopmental outcome.

At two months, maternal MLU was positively correlated with infant *Orientation* on the NBAS. Additionally, maternal positive affect was negatively correlated with the *Range of State* item but was positively correlated with the *Quality of Alertness*, *Cost of Attention*, *Examiner Facilitation*, *General Irritability* and *Robustness and Endurance* scales of the supplementary items. With regards to matched affect, matched positive affect was negatively correlated with the *Range of State* item and positively correlated with the *Cost of Attention* and *Robustness and Endurance* item. Matched neutral affect was positively correlated with the *Range of State* item and negatively correlated with the *Quality of Alertness*, *Cost of Attention*, *Examiner Facilitation* and *Robustness and Endurance* items.

At six months maternal lexical diversity was negatively associated with infant cognitive development and maternal response latency was positively associated with infant language development. At twelve months, maternal MLU was positively associated with infant motor development, maternal affect was positively associated with language development and matched neutral affect was negatively associated with language. Subsequent multiple regression analyses, with the inclusion of covariates, were carried out for each of the above models. Following this, the association between

lexical diversity and cognitive development at six months, the association between MLU and motor development and the association of positive affect and language at twelve months were statistically significant.

Two of the maternal interactive behaviour variables emerged as significant moderators of the relationship between antenatal cortisol and infant outcome. At six months, maternal total matched affect moderated the relationship between antenatal evening cortisol levels and cognitive development. Higher levels of antenatal evening cortisol were associated with lower levels of cognitive development among dyads with lower levels of overall matched affect. In dyads with average and above levels of matched affect, antenatal evening cortisol was not associated with cognitive development. At twelve months maternal *vocd* score moderated the relationship between antenatal CAR and infant motor development. A more reactive CAR in pregnancy was associated with higher levels of motor development in dyads where the mother displayed average and above levels of lexical diversity. In dyads where the mothers had lower levels of lexical diversity, antenatal CAR was not associated with infant motor development.

6.5.1 Maternal affect, matched affect and infant NBAS scores at two months

The NBAS is a measure of infant neurobehavioural development which assesses the infant's capacity to regulate their behaviour and emotional state during the administration of the test items. Infant scores on the items are grouped into five clusters and seven supplementary items, six of which were used in this study, which provide summary scores of the infant's performance across the broad domains of self-regulation, motor activity and social-orientation.

The results of this study indicate that a higher proportion of positive and matched positive affect was associated with lower scores on the *Range of State* cluster

whereas higher matched neutral affect was associated with a higher *Range of State* score. This NBAS cluster encompasses items that measure infant irritability, overall motor and crying behaviour and infant state lability. The finding that positive and matched positive affect were negatively associated with this item is contrary to previous studies reporting associations between higher levels of maternal-infant synchrony and infant self-regulation (Feldman, 1999; 2007). Although total matched affect was not significantly associated with this item, it is possible that the degree of matched neutral affect is more reflective of synchronous behaviour in interactions with infants of two months old as matched positive affect between mother and infant is not frequently observed in infants of this age-group (Feldman, 1999). However, given the fact that the converse relationship is observed in the significant relationships between maternal positive affect and a number of the supplementary items reflective of self-regulatory ability, this may be a spurious finding.

This result is also possibly reflective of the method in which the NBAS items are scored and grouped within the clusters according to the method outlined by Lester, Als and Brazelton (1982). The lability of state item within the *Range of State* cluster takes account of how many state changes are observed in the infant across the course of the examination. However, this item is not reflective of the behaviour of a number of the infants in this study who commenced the assessment in an active alert state and remained in that state for the entirety of the assessment, a feat which is reflective of advanced self-regulatory ability. As this measure was only reflective of state changes in this item, and these infants has no observed change of state, these infants could not be scored for this item. This factor may have skewed the results in this particular cluster score. Further evidence of this is that these measures of maternal and shared affect were not associated with the state regulation item in the supplementary scores which provides a summary score of infant state regulation and is more reflective of the overall ability of an infant to manage their behavioural state during the NBAS assessment.

A higher proportion of maternal positive affect was associated with higher scores in the *Quality of Alertness*, *Cost of Attention*, *Examiner Facilitation*, *General Irritability* and *Robustness and Endurance* items and higher proportions of matched positive affect were associated with the *Cost of Attention* and *Robustness and Endurance* items of the NBAS whereas matched neutral affect was negatively associated with the *Quality of Alertness*, *Cost of Attention*, *Examiner Facilitation* and *Robustness and Endurance* items. All of these items are reflective of different aspects of infant self-regulation such that higher scores are reflective of higher infant self-regulatory capacity and vice versa. These results are in line with Tronick & Gianino's (1986) Mutual Regulation Model which proposed that infants learn to regulate their biological, behavioural and emotional systems within the mother-infant relationship. The processes of matched affect and synchrony have been identified as essential aspects of mutual regulation of emotion during parent-infant interaction (Moore & Calkins, 2004) and these results are fitting with previous research reporting an association with matched affect and the development of infant emotional regulation (MacLean et al., 2014; Feldman et al., 1999; Gable & Isabella, 1992).

6.5.2 Maternal linguistic complexity and responsiveness

This study included two measures of maternal linguistic input: maternal MLU, which is a measure of maternal syntactic complexity and *vocd*, a measure of maternal lexical diversity. At two months, MLU was positively correlated with the infant *Orientation* cluster of the NBAS. At twelve months, MLU was positively associated with infant motor development. However, at six months, lexical diversity was negatively associated with infant cognitive development.

This study hypothesised that higher maternal MLU and *vocd* scores would be positively associated with infant outcome. Although this hypothesis was supported for maternal MLU, this hypothesis was not supported for maternal *vocd* score. The

relationship between maternal linguistic input and infant cognitive development has not been frequently studied within the literature, however, positive associations between maternal linguistic input and infant cognitive development have previously been reported in two studies (Murray et al., 1993; Page et al., 2010). Due to the scarcity of research on the predictive value of maternal linguistic diversity on infant cognitive development there is a difficulty in discussing how this study fits within the current literature. However, the relationship between maternal lexical diversity and infant language development may be enlightening in terms of interpreting this finding.

It is noteworthy that the research studies that most frequently report on the relationship between maternal linguistic complexity and infant language development predominately include samples of infants of approximately two years and upwards. Studies in younger infants, 18 months and below, have mainly focused on other aspects of maternal linguistic input such as the prosodic and phonological aspects of IDS. However, it is very likely that specific elements of IDS serve different functions for infants at differing stages in development. Rowe (2012) proposed that the quantity of language was more important for younger infants in the initial stages of vocabulary acquisition. A study completed by Rowe reported that the quantity of speech heard by infants of two years was a better predictor of later vocabulary, whereas at three years, the quality of language input was more important.

IDS has a lower type/token ratio in comparison to adult directed speech and mothers increase the complexity of their speech according to the age of their infants (Henning, Striano & Lieven, 2005). At six months, infants are only beginning to recognise familiar words in fluent speech (Juszyk & Aslin, 1995). It has previously been reported that infants at six months show preferences for repeat as opposed to novel utterances and demonstrate an increase in neural activity when they were presented with familiar versus unfamiliar words (McRoberts et al., 2009; Zangl & Mills, 2007). Zangl & Mills (2007) proposed that due to the limited attentional resources available to infants at six months, infants are capable of processing limited speech input and attend more

towards speech that contains familiar words. Indeed a recent study by Newman and colleagues (2016) reported that lexical diversity in maternal speech at seven months was negatively associated with infant language development at two years. Although our finding referred to a negative association between lexical diversity and cognitive development it is possible that the use of more complex language in interactions with young infants also has negative implications for emerging infant cognition.

Within this study two month MLU was positively associated with the infant *Orientation* cluster of the NBAS and at twelve months MLU was positively associated with concurrent infant motor development. Although both of these findings support the hypotheses of this study, again however there is little to no research investigating the associations between maternal linguistic behaviour and neurodevelopment in children of this age-group with which to compare these findings. There is also very little known about the patterns of MLU in infant-directed speech within the first year and the degree to which mothers adjust their utterances in accordance with infant age. Conflicting studies report that mothers increase their MLU across the first year, in line with infant age (Papousek, Papousek & Haekel, 1987), whereas others have found that maternal utterances are longer in early infancy but decline over the first year of life (Sherrod et al., 1977).

Saccani et al (2013) reported several factors of parental interaction that were predictive of motor outcome in young infants. These included: the encouragement of reaching and grasping, engaging in games about body parts and the teaching of movement words. It is possible that higher maternal MLU is reflective of greater maternal encouragement of infant action in one of the above ways. However as this study did not code the transcripts used in the study for semantic content, it is not possible to determine whether this was the case. It is suggested that future studies should investigate both the relationships between maternal MLU and that of lexical complexity in IDS during the first year, in addition to the semantic content of the

mother's speech in order to understand further about the impacts of these aspects of maternal linguistic input on the infant's emerging developmental skills.

6.5.3 Maternal Positive Affect

At twelve months, maternal positive affect was positively associated with infant language development. The association between maternal positive affect and infant development is a commonly reported finding in the developmental literature and is in keeping with numerous studies that have reported increased language skills and abilities, in addition to other neurodevelopmental outcomes, in infants of mothers who display high levels of positive affect (Steelman et al., 2002; Pearson et al., 2011; Sheinkopf et al., 2016). Sheinkopf and colleagues (2016) proposed that maternal positive affect, rather than maternal-infant matched affect which can include shared neutral affective expression, is specific to facilitating emerging infant neurodevelopment. It is proposed that maternal positive expression increases the infant's motivation to engage with their mother, resulting in more opportunities for learning experiences within dyadic interactions and the findings of this study provide additional evidence to support this. However, as there were no significant associations between maternal positive affect and the cognitive, motor, social-emotional or adaptive behaviour scales at this time-point, it may be that positive affect is uniquely related to better outcomes for infant language development rather than in other developmental domains.

6.5.4 Moderation Effect of Maternal Postnatal Interactive Behaviour

The final aim of this study sought to determine whether maternal behaviour moderated the relationship between antenatal cortisol and infant neurodevelopmental outcome. At six months, higher antenatal evening cortisol was negatively associated with

cognitive development among dyads with below the mean levels of overall matched affect. Furthermore, at twelve months, a more reactive CAR in pregnancy was associated with higher levels of motor development in dyads where the mother displayed average and above levels of lexical diversity. Within the literature, evidence is accumulating to suggest that maternal sensitivity in the postnatal period can moderate the impact of early experiences on infant neurodevelopment (e.g Schechter et al., 2017; Kaplan et al., 2008; Feldman et al., 2009). However, this study is the first to report on specific aspects of maternal behaviour which may be pertinent in this moderation effect.

At six months, a lower level of overall matched affect moderated the relationship between antenatal evening cortisol and infant cognitive development. The infant's ability to share affect with an interactive partner emerges at approximately six months and social interactions become more mutual (Feldman et al., 1996). As the infant gets older, the nature of the interactions between mother and infant evolves as the infant spends more time engaging with objects (Feldman, 1999). Therefore it is possible that maternal-infant affect at six months represents a unique time in the mother-infant relationship, a time where the both the mother and infant dyads can fully engage in the dyadic process. However, the results of this study imply that when mother-infants are unable to achieve this, it may have a corresponding negative impact on the infant's development. These findings are in line with previous work by Bergman and colleagues (2010) who reported similar findings with regards to amniotic fluid cortisol and a negative association with cognitive development but only among infants who were insecurely attached.

At twelve months, a more reactive CAR in pregnancy was associated with higher levels of motor development in dyads where the mother displayed average and above levels of lexical diversity. This moderating effect of maternal lexical diversity was unexpected, especially given the negative association between maternal *vocd* score and cognitive development at six months. However as mentioned above in the discussion

relating to the finding between maternal lexical diversity and infant development, it may be that lexical diversity serves a different function in the latter half of the first year of life. It is possible that higher diversity of linguistic input is negatively associated with infants in the first six months but moves to have a positive impact at the end of the first year. The study of infant motor development is often neglected within the field of developmental psychology. This is despite evidence that the onset or acquisition of new motor skills in infants is associated with development in cognitive, perceptual and social domains (Walle & Campos, 2013; Libertus & Hauf, 2017). In addition, parents are reported to vocalise more towards infants that walk in comparison to those that crawl (Biringen et al., 1995) and the findings of this study may be reflective of this. It is recommended that future studies include measures of infant motor development and investigate further the relationships between aspects of maternal-interactive behaviour and this domain of infant development.

One final point pertains to the interpretation of the moderation models as due to a reduced sample size in these analyses, all covariates were unable to be included in each model. A number of participants had missing values for the cortisol indices. This was a particular issue for the CAR variable as three morning saliva samples were required to calculate this variable. If the participants did not complete one morning sample, or provided insufficient saliva for analysis, we were unable to calculate the CAR for this participant. This resulted in a reduced sample size for this variable and as a result, covariates could not be included in the final model due to issues with overfitting. Given this limitation, it is suggested that the moderation models are interpreted with caution.

6.5.5 Maternal Response latency and switching pause duration

Within this study there was a significant positive relationship between maternal RL and infant language development at six months. However after controlling for

covariates, this relationship was no longer significant. In addition SP duration was not significantly associated with any of the infant developmental measures. As this study reported on maternal vocalisations as a response to infant overtures, it is possible that additional modalities through which mothers respond to their infants such as touch, or indeed a combination of both vocalisation or tactile responses, may play a more significant role in facilitating aspects of infant developmental outcome. Indeed this study also only considered maternal responses to infant non-distress vocalisations. Future studies incorporating different domains of maternal responses across a broader range of infant behaviours may provide a more complete picture of maternal responsive behaviour, which may in turn, elucidate further the relationships between maternal behaviour and infant developmental outcome.

6.5.6 Conclusions

This study reported a number of significant associations between maternal interactive behaviour and concurrent infant neurodevelopment at three time-points across the first postnatal year. The findings that maternal positive affect and maternal-infant matched affect were associated with a number of items reflective of infant self-regulatory capacity is in keeping with Tronick & Gianino's (1986) Mutual Regulation model and emphasises the maternal role in facilitating the development of infant self-regulation particularly in the early postnatal period. At six months maternal total matched affect moderated the relationship between antenatal evening cortisol and cognitive development emphasising how failure to achieve attunement within the mother-infant relationship may have a negative impact on infant development. At twelve months, maternal positive affect was positively associated with infant language development, a finding that emphasises the importance of this aspect of maternal behaviour in facilitating infant development.

Few studies have investigated the relationship between maternal linguistic complexity and development in infants of this age-group. The finding that maternal linguistic complexity was negatively associated with cognitive development at six months is a key one. Maternal speech also played a moderating role in the relationship between antenatal CAR and infant motor development to facilitate better outcome at twelve months is potentially reflective of the differing functions that aspects of infant-directed speech serve depending on the age of the child.

These findings highlight several aspects of maternal interactive behaviour that have importance for infant developmental outcome across the first year. The finding that specific aspects of maternal behaviour such as total matched affect and lexical diversity have a moderating role in the relationship between antenatal cortisol and infant neurodevelopment are of particular importance. These results contribute to the current evidence supporting the potential plasticity of the infant's brain and behavioural systems during the first year and give hopeful indications that antenatal fetal programming can potentially be modified through positive interactive experiences in the postnatal environment. The relationships between maternal linguistic input and infant motor development also highlight the need for future research to incorporate this domain of infant development into future research within this area.

Chapter 7

Discussion and Conclusions

7.1 Introduction

In this series of studies a prospective, observational and longitudinal design was used to investigate the relationship between antenatal depression, maternal hypothalamic-pituitary-adrenal (HPA) axis activity and postnatal maternal interactive behaviours and infant neurodevelopment during the first postnatal year. A sample of 100 women were recruited to this study consisting of a group of 23 women with clinically diagnosed depression, 34 women with a history of depression and a control group of 43 women with no previous history of psychiatric disorder. Mothers and their infants were followed up at two, six and twelve months postpartum. This discussion will summarise the main findings of this thesis and their context within the current literature and conclude with a summary of the strengths and limitations as well as an outline of recommendations for future research.

7.2 Antenatal depression and infant neurodevelopment

In this study, group comparisons between in the Depressed, History and Control groups indicated no differences in scores on the Neonatal Behavioural Assessment Scale (NBAS) at two months or scores in the Bayley Scale of Infant Development (BSID) at six months. At twelve months, infants in the Depressed group had lower language scores compared to controls but after controlling for concurrent depression this difference was not significant. There were no group differences in the cognitive and motor subscales of the BSID at this time-point. In the social-emotional and adaptive behaviour scales of the BSID, group differences between the history and controls were present at two months only.

The absence of differences in the NBAS measures, is contrary to the literature in this area (Diego et al., 2005; Figueiredo et al., 2017; Goodman et al., 2011; Field et al., 2001; Hernandez-Reif et al., 2006). One likely reason for the discrepancy is that in the current study, infants were assessed at eight weeks, which arguably is more

representative of infant behaviour than neonatal behaviour. It may be that group differences, observable at birth, attenuate over time as infants develop better self-regulation and control over their behaviour. A further possibility is that the NBAS becomes less sensitive in detecting differences in infant behaviour in older infants but as there are no normative data available for this measure this cannot be confirmed. To my knowledge, only one previous study has investigated the association between mothers with a history of depression and performance of their infants on the NBAS. The study completed by Suri and colleagues (2011) reported no differences between infants born to mothers with a history of depression and those with no psychiatric history which is in line with our findings.

In the current study, there were no differences in neurodevelopmental scores in both the NBAS and BSID between the infants of mothers who took antidepressants during pregnancy and those who did not. The use of antidepressants to treat antenatal depression is a controversial subject and in recent years epidemiological studies and meta-analyses have reported associations between selective serotonin reuptake inhibitor (SSRI) use and increased risk of pre-term birth and lower birthweight among other issues (Ross et al., 2013; Huybrechts et al., 2015). However these associations are inconclusive with numerous studies also reporting no increased risk of adverse outcomes for infants (Sujan et al., 2017; Margulis et al., 2013; Furu et al., 2015). Neonatal abstinence syndrome is associated with maternal SSRI usage during pregnancy and is characterised by irritability, excessive crying and tremors. This typically resolves within two weeks of birth (Rampono et al., 2009). Although some of the previous NBAS studies excluded mothers taking medication (Diego et al., 2005; Field et al., 2001; Figueiredo et al., 2017) others did not report on this (Hernandez-Reif et al., 2006) or also included mothers taking antidepressants in the control group (Goodman et al., 2011). Due to the potential confounding effects of the behaviours associated with neonatal SSRI withdrawal on NBAS outcome scores, future research in this area needs to consider this issue, particularly if assessing infants in the short period after birth

when there is a higher likelihood that these effects would be observed. Within our sample, in which a number of mothers in both the Depressed and History groups were taking SSRIs. If there were serotonin withdrawal effects, the absence of group differences in NBAS scores indicates that they have dissipated by two months.

Studies investigating the association between antenatal depression and infant and child neurodevelopment have reported inconsistent results. Some previous studies have reported findings similar to the current study, that there is no impact of maternal depression during pregnancy on infant or child outcomes (Koutra et al., 2013; Tse et al., 2010; Hay et al., 2008; Maselko et al., 2015; Husain et al., 2012). However it is possible that the group of women in this sample, who were generally highly educated and well-resourced, may not have been exposed to the additional socio-economic risk factors that are often observed in depressed pregnant women. Secondly, high levels of social support and positive paternal engagement may also have contributed to positive infant outcome. Paternal engagement with infants is strongly predictive of more positive social, behavioural, psychological and cognitive outcomes (Sarkadi et al., 2008). Although maternal depression is reported to have negative implications for all relationships within the family system, fathers have been reported to provide better parenting under conditions of high maternal distress (Emde, 1988; Vakrat et al., 2018). Future studies could potentially incorporate a standardised measurement of the mother-father relationship quality such as the *Dyadic Adjustment Scale* (Spanier, 1976) or a measurement of the father's contribution within the home. This would allow for consideration of other potential reasons for the positive outcomes in the infants born to women with antenatal depression within this sample.

There were no group differences in infant language at twelve months after controlling for postnatal maternal depressive symptoms in this study. This begs the question of whether the chronicity of symptoms leading from the antenatal period to the postnatal period has a greater impact on infant neurodevelopment than just antenatal depression alone. Recent studies, investigating the trajectory of maternal

symptoms across the perinatal period have examined the timing of perinatal depression in predicting infant neurodevelopmental outcome. Park et al (2018) identified three trajectories of maternal depressive symptoms from the antenatal period to when the children were six years. These patterns reflected mothers whose symptoms increased, decreased or remained low across this period of time. Park et al (2018) reported that the children of mothers whose depression decreased over this period had equivalent behavioural and executive function scores to those in the low symptom group, whereas those in the increasing group had poorer scores at each time-point. The pattern that the chronicity of depression constitutes a major factor for infant outcomes fits with the findings of this study. An examination of the trajectories of mean depression scores for both the Depression and History group over the period of this study (Chapter 3, Figures, 3.5, 3.6 & 3.7) indicates an overall decreasing pattern of maternal depression over the period of this study. However, mean scores may conceal considerable fluctuation of depression scores within each group. Further analyses separating those women who were depressed at particular time-points were not possible due to the limited sample size. This is a limitation of the current study and future studies with a greater number of participants could address this matter.

7.3 Antenatal cortisol and infant neurodevelopment

In this study, maternal hypothalamic-pituitary-adrenal (HPA) axis output was measured in two ways. The cortisol awakening response (CAR) is a measure of the HPA axis response to morning awakening, with a higher increase indicating a more robust response. Evening cortisol, collected twelve hours later, allows a picture of diurnal secretion to be appraised. High evening cortisol indicates potential impairment in HPA axis functioning as diurnal cortisol should have a downward slope, indicating decreasing cortisol levels across the course of the day. A healthy HPA axis is both responsive, allowing cortisol responses to challenge, and has a low level of basal secretion. Correlational analyses among the study cohort as a whole revealed significant negative

associations between two indices of the cortisol awakening response, AUCi and morning slope, and infant regulation of state at two months. The second key finding was that antenatal evening cortisol was negatively associated with infant cognitive development at six months. Thirdly, maternal CAR was positively associated with motor development at twelve months.

The literature investigating the relationship between antenatal cortisol and infant neurodevelopment demonstrate numerous inconsistencies across both methodologies and findings. The differing sampling methods used across the studies in this area adds difficulty with comparisons to the current literature. However, the HPA axis findings in the current study at two months are contrary to those who have previously examined antenatal cortisol and infant behaviour. These studies reported associations between higher cortisol and increased infant irritability, crying and negative reactivity (Davis et al., 2007; De Weerth et al., 2003; 2013; Braithwaite et al., 2017). Although the relationship between higher evening cortisol and lower cognitive development has been examined a number of times (LeWinn et al., 2009; Bergman et al., 2010; Buitelaar et al., 2003), this study is the first to find a negative association between evening cortisol levels and infant cognitive development. Buitelaar and colleagues (2003), who reported a negative association between early morning cortisol and infant cognitive and motor development, appear to be the only group, in this small literature, to have measured cortisol over the course of one day. However, this study utilised only two parameters of cortisol in their analyses, early morning cortisol, collected at 8am, irrespective of waking time, and an overall mean value of cortisol, collected from the remaining samples collected across the course of the day to 8pm.

Within our research group, Dr. Chaitra Jairaj (thesis submitted, 2017) investigated antenatal mood in relation to the CAR and the diurnal secretion of cortisol, finding no relationship between mood and cortisol measures. Higher evening cortisol levels, however, have previously been observed in women with antenatal depression (O'Keane et al., 2011) and in women exposed to stressful life events in pregnancy (Obel

et al., 2005). Outside of pregnancy, the presence of higher evening cortisol levels is also a reliable finding in patients with MDD (Vreeburg et al., 2009; Van den Bergh & Van Calster, 2009).

Our findings of a positive association between antenatal CAR and higher motor scores at twelve months are contrary to previous findings (Buitelaar et al., 2003; De Weerth et al., 2003). Outside of pregnancy a highly reactive CAR been reported in healthy populations and has been associated with better cognitive function and immune system regulation (Clow et al., 2010; Fries et al., 2009). A blunted or less reactive CAR has been associated with a myriad of health conditions such as hypertension and gastrointestinal disorders (Wirtz et al., 2007; Bohmelt et al., 2005). During pregnancy, cortisol reactivity is blunted and the CAR declines across gestation (Brunton & Russell, 2010; Entringer et al., 2010). Lower levels of waking cortisol and lower reactivity have been reported in women with antenatal depression (O'Connor et al., 2014). However, women with a history of childhood sexual abuse are reported to have a CAR that increases across gestation (Bublitz et al., 2012).

Evening cortisol levels and the CAR provide different information about HPA axis functioning and the relationship between a more reactive CAR in pregnant women and higher motor development in their infants is one of the key findings in this study. It is possible that a highly reactive CAR during pregnancy, represents a healthy cortisol response. Previous studies have reported associations between higher antenatal cortisol levels and increased fetal motor activity which is strongly associated with subsequent motor activity in neonates and across early infancy (Field et al., 2005; Di Pietro et al., 2009; Almli et al., 2001; DiPietro et al., 2008). It is possible that this relationship could be further interpreted alongside Pluess & Belsky's (2011) *prenatal programming of postnatal plasticity* hypothesis, however this will be discussed in further detail in *Section 7.6* of this discussion.

Lastly, it is important to also consider the role of other potential biological mechanisms underlying the relationship between maternal antenatal depression and

infant neurodevelopment within the first year. Genes account for approximately 50-70% of the variation in cognition in adulthood as the genetic influences on cognition are the result of accumulating environmental influences and experiences (Bouchard & McGue, 1981). However during infancy, genes account for less than 25% of the variation in cognitive ability while shared family environments account for approximately 60% (Tucker-Drob, Briley & Harden, 2013). Genetic influences on early motor development are reported to be higher, explaining up to 55% of the variance in early infant activity levels at 3 months (Goldsmith et al, 1999; Smith et al., 2017). However the influence of genes is reported to increase over the first year accounting for up to 84% of the variance of when infants take their first steps (Smith et al., 2017).

One further biological mechanism which has potential links with infant outcomes is that of the maternal immune response associated with antenatal stress. Maternal inflammatory markers, such as interleukins, may play either a direct or indirect role in fetal neuronal development (McCallister & Patterson, 2012). Associations between elevated maternal interleukins have been demonstrated to alter offspring behavioural and brain outcomes in animal models (Ponzio et al., 2007; Meyer et al., 2007). In humans, higher levels of maternal immune activation (MIA) during the antenatal period have been associated with a higher risk for autism and schizophrenia for offspring as well as depression and other affective disorders (Patterson, 2009; Ronovsky et al., 2017). Few studies have published on the link between maternal inflammatory markers in pregnancy and offspring brain development and behaviour. However, research is emerging in this field demonstrating potential links between maternal immune activation, as indexed by maternal levels of interleukin-6, and increased amygdalar volumes and connectivity to brain regions involved in learning and memory in neonates (Graham et al., 2018).

7.4 Maternal Depression and the association with postnatal interactive behaviour

Group differences were not observed between maternal MLU, lexical diversity, response latency to infant vocalisations or switching pause duration at any of the time-points in this study. At two months significantly higher shared positive and total affect were reported in the History group in comparison to Controls, a finding which was possibly attributable to the higher levels of negative affect displayed by infants within the Control group. Although there was no direct association between maternal antenatal depression and MLU, there was an indirect association which was mediated by concurrent maternal postnatal depression at two and twelve months.

Of the interactive measures used within this study, maternal-infant matched affect has the strongest body of evidence to support its association with maternal depression. However, the findings reported in the current study are contrary to those who have reported lower positive or overall matching in mother-infant dyads where the mother has depression (Field et al., 1990; Bell et al., 2004; Reck, 2011; Goodman et al., 2017). The data in the current study are also in contrast to those who have previously reported an association between maternal depression and longer maternal responses to infant overtures (Breznitz et al., 1987; Bettles, 1988; Zlochower & Cohn, 1996) but are supportive of the previous studies which have indicated no impact of maternal depression on maternal syntactic or lexical complexity (Pound et al., 1988; Righetti-Veltema et al., 2002; Cornish et al., 2008; Murray et al., 1993).

Few studies have investigated maternal sensitivity or interaction in the postnatal period in the context of antenatal depression. Goodman et al (2017) reported that even one month of clinically significant depressive symptoms during pregnancy was associated with lower maternal sensitivity postpartum. Pearson and colleagues (2012) also reported that depression in early and mid-pregnancy were associated with lower levels of maternal responsiveness. In the current study, no direct associations between maternal antenatal depression and maternal interactive behaviour across the

first year were found. In fact, only one aspect of maternal behaviour emerged as having any association with maternal depressive symptoms in the postnatal period, that of maternal mean length of utterance (MLU). This current study is unique in examining the indirect effect of maternal depression during pregnancy on maternal interaction in the postnatal period.

Although there does appear to be a higher risk of lower quality mother-infant interactions when the mother is depressed, the inconsistencies within the reported literature suggests that depression is not reliably associated with reduced maternal sensitivity or interactive behaviour (Deans, 2018; Frankel & Harmon, 1996). Indeed, numerous studies report that a substantial number of depressed mothers are able to provide a supportive framework for their infants (Field et al., 2003; Cicchetti, Rogosch & Toth, 1998). A number of factors are associated with lower maternal sensitivity or impairments within mother-infant interactions. These include: early life adversity such as exposure to childhood abuse (Kluczniok et al., 2016), lower educational attainment (Hart & Risley, 1995), parity (Shin et al., 2006), lower self-esteem (Han, 2002), lower social support (Goldstein et al., 1996) and young maternal age (Lee, 2009). All of the above factors are also associated with an increased likelihood of depression during the perinatal period also (Biaggi et al., 2015). Therefore, differences in maternal interactive behaviour may reflect factors, or interactions of factors, that are associated with maternal depression rather than being a direct effect of the depression itself.

7.5 Maternal interactive behaviour and infant neurodevelopment

The final results chapter of this thesis investigated the association between maternal postnatal interactive behaviour and infant neurodevelopmental outcome across the first year. Higher proportions of maternal positive and matched maternal-infant positive affect were associated with higher infant scores in a number of the NBAS supplementary items related to self-regulation and attentional ability and language at

twelve months. At six months, lexical complexity was negatively associated with cognitive development. Maternal MLU was positively associated with infant orientation at two months and infant motor development at twelve months.

The association between mother-infant matched positive affect and infant self-regulation and attention skills is in line with Gianino & Tronick's (1988) Mutual Regulation Model. This model proposes that infant self-regulation is fostered through affective matching in face-to-face interactions with their mother during the first months of life. Maternal positive affect was also associated with a number of items on the NBAS and infant language development at twelve months. This implies that although mutual affective matching is beneficial for infant outcome, maternal positive affect, without the necessary engagement of her infant is also of great importance. The definition of positive affect used in this study was relatively broad, encompassing maternal behaviour that included singing, playful overtures and infant directed speech (IDS). Therefore it is possible that some of the individual components of the positive affect coding, in particular IDS, had a more specific association with infant language development.

The two variables that were used as a measurement of maternal linguistic complexity, MLU and *vocd*, were also associated with different aspects of infant development in this study. The negative relationship between *vocd* and cognitive development at six months was unexpected given that maternal lexical complexity has previously been positively associated with infant neurodevelopment (Pan et al., 2005; Ramirez-Esparza et al., 2014; Campisi et al., 2009). This finding raises a question regarding the function of maternal lexical complexity within the trajectory of infant development. Lexical complexity and its positive association with infant language outcomes such as increased vocabulary has a strong evidence base in children of 24 months and upwards. However, the findings of this study suggest that increased levels of lexical complexity in maternal speech does not serve the same purpose with younger infants of six months. This is possibly due to the limited speech processing abilities of

infants of this age along with the attentional burden that diverse and complex language places of the infant's attentional resources (Zangl & Mills, 2007). Within the developmental literature, the principle of *specificity* proposes that specific aspects of parental behaviour, have specific consequences for infant outcomes at specific time-points across development (Bornstein, 2006; Vallottan et al., 2016). The findings of this study suggest that exposure of children to lexically complex language is beneficial for development in late infancy but not earlier infancy.

It is important here to highlight a potential discrepancy in the reported findings of this thesis. Despite the association between antenatal depression and lower infant language scores at twelve months and the purported evidence within the literature indicating an association between maternal linguistic input and infant language development, there were no significant associations between any of the maternal speech variables (MLU or *vocd*) and infant language development scores within this study. In addition, group differences in infant language development attenuated after controlling for concurrent maternal depression scores. However, this further emphasises that there are potentially different aspects of maternal IDS that are associated with infant language development during the first postnatal year. As mentioned in the paragraphs above, specific elements of IDS, such as prosody or pitch variation which are also indicative of maternal positive affect, may play a more important role in infant language development. Numerous studies have reported an association between maternal depression and reduced pitch variation in IDS (e.g. Porritt et al., 2014). Alternatively, a potential interaction between maternal depression and corresponding maternal IDS, be it complexity or prosody, across the first postnatal year may be what is most important in emergent infant language. Indeed, maternal speech prosody plays a role both in infant syntactical acquisition and in mapping speech sounds to meanings (Massicolte-Laforge & Shi, 2015; Estes & Hurley, 2014).

Maternal MLU was associated with higher infant orientation scores in the NBAS at two months and higher infant motor development at twelve months. In

Chapter 5 of this thesis, it was also reported that maternal MLU was the only facet of maternal interactive behaviour that was negatively associated with maternal depression. The finding of this study suggests that maternal MLU could present itself as a target behaviour to be incorporated into future research as a target of interventions within at-risk dyads. Currently, interventions exist only for the mother-infant relationship in the context of postnatal depression. These include; video-feedback to support mothers to identify infant cues and increase her sensitivity to respond them, mother-infant psychotherapy, interpersonal psychotherapy and baby massage. All have demonstrated evidence in enhancing the mother infant relationship, however the most effective interventions are those that include more than one of the above components (Stein et al., 2014; Kersten-Alvarez et al., 2011).

Recent research indicates that mothers with antenatal depressive symptoms, speak, talk and sing less to their fetuses (Hernandez-Reif et al., 2018). As newborn infants recognise their mothers voice from the womb (Descasper & Fifer, 1980) this is another potential mechanism of risk for lower cognitive and language development in these infants that could be a focus or target for future research. In another high-risk group for impaired parent-infant interaction, pre-term infants and infants admitted to the Neonatal Intensive Care Unit (NICU) and their parents, book-reading interventions have demonstrated promising evidence of better developmental outcomes for infants. Book-reading interventions are associated with better cognitive development in pre-term infants at 24 months (Braid, 2015). Participating parents also reported that the intervention helped them to feel closer to their baby (Lariviere & Rennick, 2011). Many parents are not aware of the benefits of reading to their young infants and a study of at risk mothers reported that few intended to read to their infants before 12 months of age (Lariviere & Rennick, 2011; Berkule et al., 2007). Reading to infants at a young age is instrumental in supporting a child's language and cognitive skills (Foorman et al., 2002; Rodriguez & Tamis-LeMonda, 2011) but can also encourage healthy mother-infant interaction by promoting positive engagement with the infant (Shaw et al., 2006).

Currently, there are no reported interventions that are designed to support antenatal depression or for the prevention of postnatal depression (Stein et al., 2014). Encouraging mothers to read aloud to their developing infant during pregnancy could be beneficial in improving the amount that mothers speak, and also read, to their infants in the postnatal period. It may also be of particular benefit to mothers with depression who may find it difficult to engage in spontaneous parenting behaviours such as singing or small talk (Lariviere & Rennick, 2011). Future research should consider this relatively simple intervention which could be easily implemented, cost-effective with mothers able to complete this task in their own homes.

7.6 Moderating effect of maternal interactive behaviour on infant outcome

The most important finding in this study is that of the negative association between maternal evening cortisol and infant cognitive development in mother-infant dyads with below average levels of total matched affect only. Therefore shared maternal-infant affect at six months represents a unique time in the mother-infant relationship, a time where the both the mother and infant can fully engage in the dyadic process before this relationship moves more towards being triadic as objects become more a part of this relationship. The results of this study imply that when mother-infant dyads are unable to achieve this, it may have a corresponding negative impact on the infant's development. This finding also demonstrates that it is possible that more positive or supportive mother-infant interactions in the postnatal environment can compensate for the adverse effects associated with exposure to higher levels of cortisol *in utero*. This also suggests that the programming effect of cortisol on the fetus can be moderated. This finding is in line with a previous study completed by Bergman and colleagues (2010) who also found a negative relationship between antenatal cortisol and infant cognitive development in infants of 17 months. This relationship was significant in those infants with an insecure attachment only and the negative impact

of antenatal cortisol on infant development was eliminated by a sensitive early rearing environment.

A further important finding in this study is the positive association between maternal antenatal CAR and higher motor development at twelve months in dyads where the mother used more lexical complexity in her speech. This finding provides further support that supportive maternal behaviour can alter the negative effects of an adverse prenatal environment. This finding is directly supportive of Pluess and Belsky's (2011) *Prenatal Programming of Postnatal Plasticity* hypothesis. This hypothesis proposes that antenatal adversity increases the sensitivity of the developing fetus such that environmental factors in the postnatal period influence the infant in a 'for better and for worse' manner.

The findings in this study provide the first evidence, to our knowledge, for the influence of positive environmental effects on infant developmental plasticity. This outlines that when infants are exposed to high levels of antenatal cortisol and high levels of supportive maternal care, infant outcomes will be better. However if infants are exposed to higher levels of cortisol and an environment where maternal care is less supportive, infant outcomes will be worse. The findings of the current study highlight that the early life programming of maternal care can compensate for the effects of an adverse antenatal environment. This underscores the need for appropriate intervention to support the mother or family system in situations where there is a risk to the fetus *in utero* or to the infant postnatally.

7.7 Strengths and limitations of the current study

This study reports several novel findings which have implications for future research in the areas of antenatal mental health, fetal and early life programming and their associations with infant neurodevelopment. These findings also demonstrate the importance of the mother-infant relationship and its role in infant outcomes. Additionally,

the results of this study emphasise the importance of intervening early in mother-infant dyads in situations where maternal well-being or infant development may be at risk. To my knowledge, this is the first study to use a diurnal measure of the HPA axis to investigate the relationship between antenatal cortisol and infant neurodevelopment. It is also the first study to report a positive effect of environmental influence on infant developmental plasticity.

This study has numerous strengths both in its design and its execution. The prospective aspect of this study ensured accuracy of both the maternal and infant measures that were collected. Furthermore, the observational methods used to study infant behaviour provided an objective assessment of infant development across the first postnatal year. This method is preferable to maternal report of infant development which is subject to bias thus avoiding shared method variance, a common methodological issue in developmental research.

The inclusion of women within the Depressed group in this study was based on a diagnostic interview and postnatal HAM-D scores were also completed by a registrar in psychiatry. This strength is of note as a large proportion of studies on antenatal depression use self-report questionnaires, such as the Edinburgh Postnatal Depression Scale (EPDS; Cox et al., 1987) to stratify their samples. Utilising a self-report measure on a once-off basis may indicate transient distress rather than enduring distress (Matthey & Ross-Hamid, 2012). This distinction is important as both transient and enduring depressive symptoms may have very different outcomes for both the mother and her infant. Lastly, video-recordings of mothers within their homes ensured high ecological validity and naturalistic assessment of the mother-infant relationship in comparison to recordings made within a laboratory setting.

This study is limited by its sample size, and may not be adequately powered to demonstrate group differences. Missing data also limited some aspects of the analyses used, in particular the use of covariates in a number of the regression models. The majority of women in this sample had a high level of education, with good social support

and low risk pregnancies which may limit the generalisability of the findings to the wider population.

A further limitation is the measurement of maternal depression and cortisol at only one time-point within the antenatal period restricting the ability to infer the chronicity of exposure of either variable to the developing fetus. Investigating the impact of the exposure to enduring depression or high levels of cortisol during the antenatal period may have allowed for further interpretations of the study findings and the potential consequences of chronic exposure for infant outcomes. Although, this study did assign women to each group based on the absence or presence of a clinical diagnosis of MDD, measures of self-report depression were used within a number of the analyses. It is important to highlight again the limitations regarding self-report measures of depression which may indicate transient distress rather than enduring distress but may also fail to identify women who meet the criteria for a clinical diagnosis of MDD within the postnatal period (Matthey & Ross-Hamid, 2012; Pawlby et al., 2008).

This study also did not include any pregnancy specific measures of maternal antenatal distress. This could have potentially led to an underestimation of the extent of stress the women in this study experienced during their pregnancy. Previous authors have implied that it is possible that pregnancy related distress may be a particularly potent form of stress, particularly in the prediction of birth and offspring outcomes (Lobel et al., 2008). The inclusion of some pregnancy-specific measures of maternal distress, such as the *Prenatal Distress Questionnaire* (Yali & Lobel, 1999) or the *Pregnancy Specific Anxiety Scale* (Wadhwa et al., 1993), in future research will allow further elucidation of the association between MDD in pregnancy, pregnancy specific stress and infant outcomes.

Moreover, due to the collection of salivary cortisol by participants in their homes, it is possible that this may have introduced elements of sampling error into our cortisol measures. Potential errors that can occur using this method include; eating or drinking before sample collection, errors in collection time and failure to follow the

protocol correctly. Lastly, inter-rater reliability for maternal neutral affect was low at two months. This is most likely a result of the use of only one video camera meaning that the mothers face was sometimes obscured during the recordings, thus making the interaction more difficult to code. As a result, the analyses which included maternal neutral affect must be interpreted with caution.

7.8 Future Directions

As of yet, there is no consensus about the impact of antenatal depression on infant neurodevelopmental outcome. Further studies which are adequately powered and control for known confounding variables are required. Of particular importance is the necessity for research in younger infants as this currently represents a huge gap in the literature.

Further exploration of the relationship between the maternal HPA axis and infant neurodevelopment are needed. Of more importance is the need to address the issue of cortisol measurement. Attempts to make comparisons between studies or generalise findings from this area are futile due to the inconsistencies and methodological issues in this literature. It is recommended that measurement of CAR/diurnal cortisol becomes standard as this yields a measure of basal HPA axis activity across the diurnal cycle in addition to HPA axis responsivity. It is recommended that the guidelines suggested by the *International Society of Psychoneuroendocrinology* (Stalder et al., 2016) regarding the collection of cortisol parameters are adhered to in future studies employing the measurement of antenatal cortisol.

There is no doubt that the human nervous system are most plastic in early life (Johnson et al., 2016; Pujol et al., 2006). Therefore it is of paramount importance that more specific aspects of maternal behaviour that reliably predict positive infant development outcomes are identified. This will allow for the development of targeted interventions which can be employed in at risk populations. Our findings, for example,

suggest that positive mother-infant interaction may compensate for the effects of an adverse antenatal environment. Replication of this finding would provide further evidence for a form of intervention targeting maternal sensitivity. It would also be of interest if future studies could incorporate measures of methylation at key genes in the HPA axis to determine if any poor outcomes are reflected in the epigenome. Currently little is known about possible epigenetic changes across development.

Lastly, within research, more consideration needs to be given to the role that fathers play in the life of the infant but also as a source of support for the mother. Active and regular engagement with fathers positively predicts a range of developmental outcomes (Sarkadi et al., 2008). It is possible that supportive fathers could also moderate the association between antenatal or postnatal depression and infant neurodevelopment. Conversely, maternal depression is also associated with increased likelihood of paternal depression and higher levels of parenting stress (Goodman, 2008). This may imply further developmental risk for the child and must be considered for studies in the future.

7.9 Conclusions

The absence of group differences in infant neurodevelopment between the Depressed, History and Control groups within this study implies that maternal antenatal depression is not reliably associated with adverse outcomes for the infant. However the relationships between antenatal HPA axis measures and infant neurodevelopment provides clear evidence of a programming effect of maternal cortisol levels on the developing fetus during pregnancy.

Investigation of the relationship between maternal antenatal, postnatal depression and maternal interactive behaviour indicated that, across the first year of life, maternal mood is associated with lower syntactical complexity (MLU) in the speech mothers' use with their infants. However, this suggests that maternal MLU may serve

as target behaviour for future research and interventions where the mother-infant dyad are at risk of adverse outcomes.

The associations between maternal positive affect, maternal-infant matched affect and the self-regulatory items of the NBAS at two months, provide evidence of the importance of the maternal role in the development of infant self-regulation ability. The relationships between maternal MLU, lexical complexity (*vocd*) and positive affect with different aspects of infant neurodevelopment supports the principle of *specificity* proposed within developmental theory. These findings emphasise the importance of sensitive and supportive maternal behaviour during interactions with her infant and the role that these behaviours play in supporting infant development. These findings also highlight that specific parental behaviours may serve different functions for infant development at different developmental stages.

Lastly and most importantly, maternal behaviour moderated the relationship between antenatal cortisol and infant neurodevelopment in a 'for-better *and* for-worse' manner, indicating that more optimal levels of maternal interactive behaviour are associated with better infant outcomes. These findings highlight that maternal care can compensate for the effects of an adverse antenatal environment. This underscores the need for appropriate intervention to support the mother or family system in situations where there is a risk to the fetus *in utero* or to the infant postnatally. Further investigation of the characteristics of the fetal and early life environment may provide better insight as to the potential factors which can impair or indeed support optimum mother and infant outcome across the perinatal period.

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Appendices

Appendix I: Study Information Flyer



Trinity College Dublin
Coláiste na Tríonóide, Baile Átha Cliath
The University of Dublin



Call for pregnant women to participate in clinical study on stress/depression during pregnancy

We need your help...

A study of the stress hormone (cortisol) in women and their babies



Pregnancy can be a stressful time for many women. The body normally responds to stress by secreting cortisol, a stress hormone. In this study we are measuring cortisol to see if this reflects how stressed a pregnant woman may feel. We also want to see how your baby's stress hormone levels change in the first year after birth.

You are suitable if...

- You are stressed/depressed
- You are **not** stressed/depressed

Your role in the study...

- Assessment with Dr Chai Jairaj during your pregnancy
- Providing saliva samples and one blood sample for measurement of stress hormone levels during your pregnancy



Your baby's role in the study...

- Saliva samples will be collected from your baby at 8 weeks, 6 months, and one year after birth
- Baby's development and play activity will be observed with a 5-minute video, to be analysed by experienced Psychologists



Benefits...

- **€30 travel reimbursement** for taking part in the study!
- **FREE** developmental and behavioural assessments for your baby in the first year
- Regular contact with Psychiatrist if required and referrals to the service as necessary
- Assisting in medical research by helping us to better understand the development of depression and to improve the treatment and prevention of depression for future generations

If you wish to participate in this study, please contact in confidence...

Dr Chai Jairaj (Registrar in Psychiatry): cjairaj@tcd.ie **086 370 1387**

Appendix II: Participant Information Sheet



INFORMATION FOR PATIENTS on research study

Depression during pregnancy: a study of stress hormone systems in women and their babies

Thank you for taking the time to read this Information Sheet. We would be most grateful if you would consider taking part in our research project.

This study is being organized by **Professor Veronica O'Keane** from Trinity College Dublin; and **Professor Eleanor Molloy**, Consultant Neonatologist in Coombe Women and Infants University Hospital & **Professor Fionnuala McAuliffe**, Consultant Obstetrician in the National Maternity Hospital. This project has approval from the Research Ethics Committee in both the Coombe Women and Infants University Hospital and the National Maternity Hospital.

What is the Research Project about?

Basically, we are looking at the effects of depression during pregnancy on the woman's body and on the developing baby. Feeling stressed is a normal human experience but feeling stressed and sad over a long period of time is what we loosely call depression. Sleep, appetite and energy changes are also usually present. Depression during pregnancy can often be neglected because there is an idea that if you suffer through your pregnancy, it will all end when your baby is born. Unfortunately, depression often does not go away, and can even get worse, after baby is born. About half of what we call postnatal depression actually starts during pregnancy.

We want to study two main issues. First, we want to see if depression during pregnancy is having an effect on the stress hormone systems of pregnant women by measuring the amount of the stress hormone cortisol in saliva. We also would like to take one blood sample to measure possible immune changes: immune function is suppressed by stress. The stress/immune systems can change the way genes work; this process is called epigenetics and this will be measured also in saliva samples.

Second, we want to see if this affects the baby's stress/immune/epigenetic systems after he/she is born. In other words, does the stress from the pregnant women cause changes to baby's stress systems? We wish to look at cortisol levels in baby's saliva at their vaccinations (at 2 months, 6 months and 1 year).

Why am I being asked to participate in this research project?

For our research study, we are looking for pregnant women who feel stressed/depressed and also those who feel well. You will not directly benefit from participation in this study but the findings from the study will help us to understand what is happening in depression during pregnancy and open up new pathways to treat depression during pregnancy.

What would my role be in this Research Project?

Dr Chai Jairaj will talk you through the study, and explain what is involved.

Basically, we would like to measure your stress/immune function at the six-month (25 weeks) time-point during pregnancy.

What is specifically involved for you?

We would like to:

1. Talk to you about your level of stress/depression and fill in some scales: this will take about 40 min.
2. Take some saliva samples to measure stress hormones. We will give you instructions about taking the saliva samples.
3. Take a blood sample to measure immune markers. We will collect the blood and saliva at the 6-month time point in pregnancy.

What is specifically involved for your baby?

Dr Jairaj will text you following the birth of your baby.

1. To measure baby cortisol secretion we will take saliva samples before and 30 minutes after your baby's vaccination injections. Baby saliva is collected by placing a swab under your baby's tongue for two minutes. Niamh O'Leary, our baby research worker will meet you at your baby's vaccination appointment at 2 months, 6 months and 12 months to take this sample.
2. We may also take a saliva sample from you and your baby at six months to look for any differences between mother and baby in a specific gene (epigenetics).
3. We would also like to look at baby development and interaction at each time point. At 7 weeks we will look at baby development using the Neonatal Behavioral Assessment Scale (NBAS) which shows us about baby reflexes and emerging interaction skills. At 6 and 12 months we will look at your baby's emerging thinking, language and motor skills using the Bayley Scale of Infant Development (BSID). We will also take a 3-minute video of you interacting or playing with your baby at each time point. Your details will be kept entirely confidential and this video will only be used for the purpose of the study. If there are any concerns, a report of the video session or infant assessments may be shared with medical practitioners with parental consent.

What are the possible risks, discomforts, side effects or inconveniences?

Should the questionnaires reveal that you are depressed you will be offered the option of referral to a specialist perinatal psychiatry service in the hospital or your local psychiatrist to discuss possible treatment options.

What measures will be taken to ensure confidentiality?

You will be given a study number and all your information will be stored using this number, and so will be anonymous. All the saliva and blood samples that we collect from you will be stored and analysed anonymously.

Is there likely to be a benefit to me or will there be potential benefits to improve future medical care?

There is a wide variation in cortisol levels in healthy people, and the same is true during pregnancy. Your cortisol levels are unlikely to tell us anything about how stressed you are as an

individual as we do not know enough about pregnancy, depression and cortisol hormones to be able to judge your level as normal or not. This is one question that we hope to answer with this study.

If we show that depression in women during pregnancy is changing the developing baby's stress systems, it has very important consequences for the future health of babies. It is important to know how depression affects mother and baby if we wish to look at treatments for depression in pregnant women and "soothing therapies" for their babies.

At the completion of the project, will I be informed of the research outcome?

Yes, we will ask you whether you want to know the results from our project and we will send you on copies of our reports and publications when they are ready.

More Information?

You may wish to discuss participation in this research project with your family and/or with your doctor. Please feel free to ask for further information before deciding if you will take part.

Consent

You may, of course, withdraw from the study at any point and this will not change the care that you receive in any way.

My rights as a Participant

1. I am informed that no information regarding my medical history will be divulged and the results of any tests involving myself will not be published so as to reveal my identity.
2. The detail of the procedure proposed has also been explained to me, including the anticipated length of time it will take, the frequency with which the procedure will be performed and an indication of any discomfort which may be expected.
3. Although I understand that the purpose of this research project is to improve the quality of medical care, it has also been explained that my involvement may not be of any benefit to myself.
4. I have been given the opportunity to have a member of my family or a friend present while the project was explained to me.
5. I understand that this research project has been approved by the Research Ethics Committee of the National Maternity Hospital
6. I have received a copy of this document for my records

Name and phone number of emergency contact:

Dr Chai Jairaj

086 370 1387

Appendix III: Participant Consent Form



Consent Form for **REDEEM** study

Depression during pregnancy: a study of stress hormone systems in women and their babies

Principal Investigators: Professor Fionnuala McAuliffe, Professor Eleanor Molloy, Professor Veronica O'Keane

I have read the Information Leaflet and it has been explained to me by

_____.

I understand the Information Sheet and have had time to consider my participation in the study. I have this Information Sheet to keep and I understand the purpose, extent and possible effects of my involvement. I have been asked whether I would like to have a family member or friend present while this project was being explained to me.

I understand that it is my decision to take part in the study and that if I decide to withdraw from the study at any time without explanation, this will not affect my access to the best available treatment and care from the National Maternity Hospital/Coombe Mother & Infant's University Hospital.

Signed _____ Date _____

Print name _____

Witnessed by _____ Date _____

Print name _____

If you have any concerns or questions regarding the study, please contact:

Dr Chai Jairaj

086 370 1387

Appendix IV: Participant Saliva Instructions

Participant Step-by-Step Instructions

Saliva Sample Collection

- The purpose of the saliva collection is to measure the changes in stress hormones throughout the day.
- The saliva will be collected by placing the swab provided under your tongue for 1-2 minutes after which you will place the swab in the tube provided. Please see detailed instructions below.
- The tubes will be labelled with time points corresponding to each collection after waking.
- You will have **5 collections** in total. You should put them in the plastic bag provided and place the samples in the refrigerator.
- Please **post the tubes to Dr Chai Jairaj in Trinity College Dublin in the pre-stamped and addressed envelope provided.**

The tubes will be labelled for the specific times below. Please collect saliva at each of these consecutive times after waking for **one** day.

1. 0 minutes (on waking)
2. 30 minutes (after waking)
3. 60 minutes (after waking)
4. 12 hours (after waking, in the pm)
5. 12.5 hours (after waking, in the pm)

For example, if you wake up at 7.00 am, you will be collecting samples at:

1. 7.00 am (approximately)
2. 7.30 am
3. 8.00 am
4. 7.00 pm
5. 7.30 pm

How to take samples:

Take the tube marked with the appropriate time point, remove the blue cap on the tube and then remove the swab in the smaller tube. Place the swab under your tongue for 1-2 minutes. Then return the saturated swab into the smaller tube and close it firmly with the blue top. Please ensure that the saturated swab is placed in the smaller tube that clicks into the larger tube. Place all samples in the refrigerator until you post them.

Please do not brush your teeth prior to collecting the morning samples. Please rinse your mouth out with water 5 min before taking a sample (Please make sure that you only collect saliva and not water from rinsing your mouth out!) If you forget to take a sample, just move on to the next time point.

If you have any questions, please contact Dr Chai Jairaj at 086 370 1387

Appendix V: MINI International Neuropsychiatric Interview

A. MAJOR DEPRESSIVE EPISODE

(MEANS : GO TO THE DIAGNOSTIC BOXES, CIRCLE NO IN ALL DIAGNOSTIC BOXES, AND MOVE TO THE NEXT MODULE)

A1	Have you been consistently depressed or down, most of the day, nearly every day, for the past two weeks?	NO	YES
A2	In the past two weeks, have you been much less interested in most things or much less able to enjoy the things you used to enjoy most of the time?	NO	YES
	IS A1 OR A2 CODED YES?	NO	YES

A3 Over the past two weeks, when you felt depressed or uninterested:

- a Was your appetite decreased or increased nearly every day? Did your weight decrease or increase without trying intentionally (i.e., by $\pm 5\%$ of body weight or ± 8 lbs. or ± 3.5 kgs., for a 160 lb./70 kg. person in a month)?
IF YES TO EITHER, CODE YES.
- b Did you have trouble sleeping nearly every night (difficulty falling asleep, waking up in the middle of the night, early morning waking or sleeping excessively)?
- c Did you talk or move more slowly than normal or were you fidgety, restless or having trouble sitting still almost every day?
- d Did you feel tired or without energy almost every day?
- e Did you feel worthless or guilty almost every day?
- f Did you have difficulty concentrating or making decisions almost every day?
- g Did you repeatedly consider hurting yourself, feel suicidal, or wish that you were dead?

ARE 5 OR MORE ANSWERS (A1-A3) CODED YES?

NO YES *

**MAJOR DEPRESSIVE
EPISODE, CURRENT**

IF PATIENT HAS CURRENT MAJOR DEPRESSIVE EPISODE CONTINUE TO A4,
OTHERWISE MOVE TO MODULE B:

- A4 a During your lifetime, did you have other episodes of two weeks or more when you felt depressed or uninterested in most things, and had most of the problems we just talked about?

- b In between 2 episodes of depression, did you ever have an interval of at least 2 months, without any depression and any loss of interest?

NO YES

**MAJOR DEPRESSIVE
EPISODE, RECURRENT**

* If patient has Major Depressive Episode, Current, use this information in coding the corresponding questions on page 5 (A6d, A6e).

MAJOR DEPRESSIVE EPISODE WITH MELANCHOLIC FEATURES (optional)

(MEANS : GO TO THE DIAGNOSTIC BOX, CIRCLE NO, AND MOVE TO THE NEXT MODULE)

IF THE PATIENT CODES POSITIVE FOR A CURRENT MAJOR DEPRESSIVE EPISODE (A3 = YES), EXPLORE THE FOLLOWING:

A5 a	During the most severe period of the current depressive episode, did you lose almost completely your ability to enjoy nearly everything?	NO	YES
b	During the most severe period of the current depressive episode, did you lose your ability to respond to things that previously gave you pleasure, or cheered you up? IF NO: When something good happens does it fail to make you feel better, even temporarily?	NO	YES
	IS EITHER A5a OR A5b CODED YES?	NO	YES

A6 Over the past two week period, when you felt depressed and uninterested:

a	Did you feel depressed in a way that is different from the kind of feeling you experience when someone close to you dies?	NO	YES
b	Did you feel regularly worse in the morning, almost every day?	NO	YES
c	Did you wake up at least 2 hours before the usual time of awakening and have difficulty getting back to sleep, almost every day?	NO	YES
d	IS A3c CODED YES (PSYCHOMOTOR RETARDATION OR AGITATION)?	NO	YES
e	IS A3a CODED YES FOR ANOREXIA OR WEIGHT LOSS?	NO	YES
f	Did you feel excessive guilt or guilt out of proportion to the reality of the situation?	NO	YES

ARE 3 OR MORE A6 ANSWERS CODED YES?

NO YES

*Major Depressive Episode
with
Melancholic Features
Current*

B. DYSTHYMIA

(MEANS : GO TO THE DIAGNOSTIC BOX, CIRCLE NO, AND MOVE TO THE NEXT MODULE)

IF PATIENT'S SYMPTOMS CURRENTLY MEET CRITERIA FOR MAJOR DEPRESSIVE EPISODE, DO NOT EXPLORE THIS MODULE.

B1	Have you felt sad, low or depressed most of the time for the last two years?	NO	YES
B2	Was this period interrupted by your feeling OK for two months or more?	NO	YES
B3	During this period of feeling depressed most of the time:		
a	Did your appetite change significantly?	NO	YES
b	Did you have trouble sleeping or sleep excessively?	NO	YES
c	Did you feel tired or without energy?	NO	YES
d	Did you lose your self-confidence?	NO	YES
e	Did you have trouble concentrating or making decisions?	NO	YES
f	Did you feel hopeless?	NO	YES
	ARE 2 OR MORE B3 ANSWERS CODED YES?	NO	YES

B4Did the symptoms of depression cause you significant distress or impair your ability to function at work, socially, or in some other important way?

NOYES

DYSTHYMIA

CURRENT

C. SUICIDALITY

In the past month did you:

		NO	YES	Points
C1	Suffer any accident?			0
	IF NO TO C1, SKIP TO C2; IF YES, ASK C1a,:			
C1a	Plan or intend to hurt yourself in that accident either passively or actively?			0
	IF NO TO C1a, SKIP TO C2; IF YES, ASK C1b,:			
C1b	Did you intend to die as a result of this accident?			0
C2	Think that you would be better off dead or wish you were dead?			1
C3	Want to harm yourself or to hurt or to injure yourself?			2
C4	Think about suicide?			6

IF YES, ASK ABOUT THE INTENSITY AND FREQUENCY OF THE SUICIDAL IDEATION:

Frequency	Intensity			
Occasionally	Mild	→	Can you control these impulses and state that you will not act on them while in this program? Only score 8 points if response is NO.	NO YES 8
Often	Moderate			
Very often	Severe			
C5	Have a suicide plan?		NO YES	8
C6	Take any active steps to prepare to injure yourself or to prepare for a suicide attempt in which you expected or intended to die?		NO YES	9
C7	Deliberately injure yourself without intending to kill yourself?		NO YES	4
C8	Attempt suicide?		NO YES	10
	Hoped to be rescued / survive			
	Expected / intended to die			

In your lifetime:

C9	Did you ever make a suicide attempt?	NO	YES	4

IS AT LEAST 1 OF THE ABOVE (EXCEPT C1) CODED YES?

IF YES, ADD THE TOTAL NUMBER OF POINTS FOR THE ANSWERS (C1-C9) CHECKED 'YES' AND SPECIFY THE LEVEL OF SUICIDE RISK AS INDICATED IN THE DIAGNOSTIC BOX:

MAKE ANY ADDITIONAL COMMENTS ABOUT YOUR ASSESSMENT OF THIS PATIENT'S CURRENT AND NEAR FUTURE SUICIDE RISK IN THE SPACE BELOW:

NO	YES
SUICIDE RISK	
CURRENT	
1-8 points	Low
9-16 points	Moderate
≥ 17 points	High

Appendix VI: Hamilton Rating Scale for Depression (HAM-D)

THE HAMILTON RATING SCALE FOR DEPRESSION

(to be administered by a health care professional)

Patient's Name _____

Date of Assessment _____

To rate the severity of depression in patients who are already diagnosed as depressed, administer this questionnaire. The higher the score, the more severe the depression.

For each item, write the correct number on the line next to the item. (Only one response per item)

- _____ **1. DEPRESSED MOOD** (Sadness, hopeless, helpless, worthless)
0= Absent
1= These feeling states indicated only on questioning
2= These feeling states spontaneously reported verbally
3= Communicates feeling states non-verbally—i.e., through facial expression, posture, voice, and tendency to weep
4= Patient reports VIRTUALLY ONLY these feeling states in his spontaneous verbal and non-verbal communication
- _____ **2. FEELINGS OF GUILT**
0= Absent
1= Self reproach, feels he has let people down
2= Ideas of guilt or rumination over past errors or sinful deeds
3= Present illness is a punishment. Delusions of guilt
4= Hears accusatory or denunciatory voices and/or experiences threatening visual hallucinations
- _____ **3. SUICIDE**
0= Absent
1= Feels life is not worth living
2= Wishes he were dead or any thoughts of possible death to self
3= Suicidal ideas or gesture
4= Attempts at suicide (any serious attempt rates 4)
- _____ **4. INSOMNIA EARLY**
0= No difficulty falling asleep
1= Complains of occasional difficulty falling asleep—i.e., more than 1/2 hour
2= Complains of nightly difficulty falling asleep
- _____ **5. INSOMNIA MIDDLE**
0= No difficulty
1= Patient complains of being restless and disturbed during the night
2= Waking during the night—any getting out of bed rates 2 (except for purposes of voiding)

Adapted from Hedlung and Vieweg, The Hamilton rating scale for depression, *Journal of Operational Psychiatry*, 1979;10(2):149-165.

-
- _____ **6. INSOMNIA LATE**
0= No difficulty
1= Waking in early hours of the morning but goes back to sleep
2= Unable to fall asleep again if he gets out of bed
- _____ **7. WORK AND ACTIVITIES**
0= No difficulty
1= Thoughts and feelings of incapacity, fatigue or weakness related to activities; work or hobbies
2= Loss of interest in activity; hobbies or work—either directly reported by patient, or indirect in listlessness, indecision and vacillation (feels he has to push self to work or activities)
3= Decrease in actual time spent in activities or decrease in productivity
4= Stopped working because of present illness
- _____ **8. RETARDATION: PSYCHOMOTOR** (Slowness of thought and speech; impaired ability to concentrate; decreased motor activity)
0= Normal speech and thought
1= Slight retardation at interview
2= Obvious retardation at interview
3= Interview difficult
4= Complete stupor
- _____ **9. AGITATION**
0= None
1= Fidgetiness
2= Playing with hands, hair, etc.
3= Moving about, can't sit still
4= Hand wringing, nail biting, hair-pulling, biting of lips
- _____ **10. ANXIETY (PSYCHOLOGICAL)**
0= No difficulty
1= Subjective tension and irritability
2= Worrying about minor matters
3= Apprehensive attitude apparent in face or speech
4= Fears expressed without questioning
- _____ **11. ANXIETY SOMATIC:** Physiological concomitants of anxiety, (i.e., effects of autonomic overactivity, "butterflies," indigestion, stomach cramps, belching, diarrhea, palpitations, hyperventilation, paresthesia, sweating, flushing, tremor, headache, urinary frequency). Avoid asking about possible medication side effects (i.e., dry mouth, constipation)
0= Absent
1= Mild
2= Moderate
3= Severe
4= Incapacitating
-

-
- _____ **12. SOMATIC SYMPTOMS (GASTROINTESTINAL)**
0= None
1= Loss of appetite but eating without encouragement from others. Food intake about normal
2= Difficulty eating without urging from others. Marked reduction of appetite and food intake
- _____ **13. SOMATIC SYMPTOMS GENERAL**
0= None
1= Heaviness in limbs, back or head. Backaches, headache, muscle aches. Loss of energy and fatigability
2= Any clear-cut symptom rates 2
- _____ **14. GENITAL SYMPTOMS** (Symptoms such as: loss of libido; impaired sexual performance; menstrual disturbances)
0= Absent
1= Mild
2= Severe
- _____ **15. HYPOCHONDRIASIS**
0= Not present
1= Self-absorption (bodily)
2= Preoccupation with health
3= Frequent complaints, requests for help, etc.
4= Hypochondriacal delusions
- _____ **16. LOSS OF WEIGHT**
A. When rating by history:
0= No weight loss
1= Probably weight loss associated with present illness
2= Definite (according to patient) weight loss
3= Not assessed
- _____ **17. INSIGHT**
0= Acknowledges being depressed and ill
1= Acknowledges illness but attributes cause to bad food, climate, overwork, virus, need for rest, etc.
2= Denies being ill at all
- _____ **18. DIURNAL VARIATION**
A. Note whether symptoms are worse in morning or evening. If NO diurnal variation, mark none
0= No variation
1= Worse in A.M.
2= Worse in P.M.
B. When present, mark the severity of the variation. Mark "None" if NO variation
0= None
1= Mild
2= Severe
-

-
- _____ **19. DEPERSONALIZATION AND DEREALIZATION** (Such as: Feelings of unreality;
Nihilistic ideas)
0= Absent
1= Mild
2= Moderate
3= Severe
4= Incapacitating
- _____ **20. PARANOID SYMPTOMS**
0= None
1= Suspicious
2= Ideas of reference
3= Delusions of reference and persecution
- _____ **21. OBSESSIONAL AND COMPULSIVE SYMPTOMS**
0= Absent
1= Mild
2= Severe

Total Score _____

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Web site: www.glaxowellcome.com

Appendix VII: Center for Epidemiological Studies Depression Scale (CES-D)

Center for Epidemiological Studies Depression Scale (CES-D), NIMH

Name: _____

Age: _____

Gender: _____ Male _____ Female

	During the Past Week			
	Rarely or none of the time (less than 1 day)	Some or a little of the time (1-2 days)	Occasionally or a moderate amount of time (3-4 days)	Most or all of the time (5-7 days)
1. I was bothered by things that usually don't bother me.				
2. I did not feel like eating; my appetite was poor.				
3. I felt that I could not shake off the blues even with help from my family or friends.				
4. I felt I was just as good as other people.				
5. I had trouble keeping my mind on what I was doing.				
6. I felt depressed.				
7. I felt that everything I did was an effort.				
8. I felt hopeful about the future.				
9. I thought my life had been a failure.				
10. I felt fearful.				
11. My sleep was restless.				
12. I was happy.				
13. I talked less than usual.				
14. I felt lonely.				
15. People were unfriendly.				
16. I enjoyed my life.				
17. I had crying spells.				
18. I felt sad.				
19. I felt that people dislike me.				
20. I could not get "going."				

Appendix VIII: Perceived Stress Scale (PSS)

PSS

Name: _____

Age: _____

The questions in this scale ask you about your feelings and thoughts during the last month. In each case, you will be asked to indicate *how often* you felt or thought a certain way. Although some of the questions are similar, there are differences between them and you should treat each one as a separate question. The best approach is to answer each question fairly quickly. That is, don't try to count up the number of times you felt a particular way, but rather indicate the alternative that seems like a reasonable estimate.

In the last month...	0 Never	1 Almost Never	2 Some- times	3 Fairly Often	4 Very Often
1. How often have you been upset because of something that happened unexpectedly?					
2. How often have you felt that you were unable to control the important things in your life?					
3. How often have you felt nervous and "stressed"?					
4. How often have you dealt successfully with irritating life hassles?					
5. How often have you felt that you were effectively coping with important changes that were occurring in your life?					
6. How often have you felt confident about your ability to handle your personal problems?					
7. How often have you felt that things were going your way?					
8. How often have you found that you could not cope with all the things that you had to do?					
9. How often have you been able to control irritations in your life?					
10. How often have you felt that you were on top of things?					
11. How often have you been angered because of things that happened that were outside of your control?					
12. How often have you found yourself thinking about things that you have to accomplish?					
13. How often have you been able to control the way you spend your time?					
14. How often have you felt difficulties were piling up so high that you could not overcome them?					

Appendix IX: Neonatal Behavioural Assessment Scale (NBAS) scoring form

NBAS SCORING FORM

Baby Name.....Date of Assessment..... Examiner.....

Sex..... dob..... Gestational age..... Birthweight..... ..Height.....HC..... Mode of delivery.....

Length of Labour.....Apgar scores..... ..Parity..... ..Type of feeding.....

Infant Behaviour

Habituation	9	8	7	6	5	4	3	2	1	Comments
Response dec. to light										
Response dec. to rattle										
Response dec. to bell										
Res. dec. to foot probe										

Social-Interactive	9	8	7	6	5	4	3	2	1	Comments
Animate visual										
Animate visual & auditory										
Inanimate visual										
Inanimate visual & auditory										
Inanimate auditory										
Animate auditory										
Alertness										

Motor System	9	8	7	6	5	4	3	2	1	Comments
General tone										
Motor maturity										
Pull- to-sit										
Defensive										
Activity level										

State Organisation	9	8	7	6	5	4	3	2	1	Comments
Peak of excitement										
Rapidity of build- up										
Irritability										
Lability of states										

State Regulation	9	8	7	6	5	4	3	2	1	Comments
Cuddliness										
Consolability										
Self-quieting										
Hand-to-mouth										

Autonomic System	9	8	7	6	5	4	3	2	1	Comments
Tremulousness										
Startles										
Lability of skin colour										

Smiles ☐

Supplementary Items	9	8	7	6	5	4	3	2	1	Comments
Quality of alertness										
Cost of attention										
Examiner facilitation										
General irritability										
Robustness & endurance										
State regulation										
E's emotional response										

Reflexes	0	1	2	3	Asym	Comments
Plantar						
Babinski						
Ankle clonus						
Rooting						
Sucking						
Glabella						
Passive resist - legs						
Passive resist - arms						
Palmar (hand grasp)						
Placing						
Standing						
Walking						
Crawling						
Incurvation						
Tonic dev. - head & eyes						
Nystagmus						
TNR						
Moro						

SUMMARY : INFANT	
Strengths	Concerns

SUMMARY : PARENT(S)	
Strengths	Concerns

RECOMMENDATIONS FOR CAREGIVING:-

Appendix X: Maternal and Infant Affect Scoring System

2 Months	Positive Affect	Neutral Affect	Negative Affect
Mother	- Smiling, laughing or playful face (e.g. mock surprise, exaggerated emotional displays e.g pretend crying) directed towards infant. OR - Neutral <u>facial</u> affect accompanied by infant-directed speech (animated, high pitched tone) singing or noises directed at infant (e.g. kissing noises)	- Onset of a neutral facial expression AND/OR - Vocalising using a whisper (without obvious positive or negative facial affect) or a shushing or shhhhh sound. AND/OR - Mother is commenting on what is going on in a neutral tone.	Facial expression or vocalisation indicating sadness, anger, annoyance, irritation or sarcasm (e.g. saying positive or neutral words with a mocking tone)
Infant	Smiling, laughter, squealing, cooing, babbling or any positive affective vocalisations or utterances that signal engagement with the mother. AND/OR	- No display of interest/orientation towards mother or activity. OR - Engaged in activity with neutral affect.	- Facial expression such as frown, furrowed eyebrows, or vocalisation indicating distress, discomfort, sadness, protest, cry or fuss. - Infant startles due to mother's behaviour (e.g. mother's tone of

	Displays motor behaviour that signals engagement and/or excitement directed towards mother or activity (e.g raising eyebrows, kicking legs or moving arms in a relaxed not rigid manner)	OR Gaze is directed towards mother, toy or activity with no strong affect either positive or negative (e.g. holding toy, looking at mother with neutral facial expression)	voice too loud, mother shakes a rattle too close to infant's face) and not due to something extraneous to the interaction (e.g. doorbell ringing, interruption from sibling etc). Infant deliberately avoids gaze or turns head to look away from mother or toy that she presents (not due to an engagement with something else). Infant displays motor behaviour that indicates that he/she is uncomfortable (e.g. rigid arms, twisting away from mother, arching back)

6 Months	Positive Affect	Neutral Affect	Negative Affect
Mother	- Smiling, laughing or playful face (e.g. mock surprise, exaggerated emotional displays e.g pretend crying) directed towards infant. OR - Neutral <u>facial</u> affect accompanied by infant-directed speech (animated, high pitched tone) singing or noises directed at infant (e.g. kissing noises)	- Onset of a neutral facial expression AND/OR - Vocalising using a whisper (without obvious positive or negative facial affect) or a shushing or shhhhhh sound. AND/OR - Mother is commenting on what is going on in a neutral tone.	Facial expression or vocalisation indicating sadness, anger, annoyance, irritation or sarcasm (e.g. saying positive or neutral words with a mocking tone)
Infant	Smiling, laughter, squealing, cooing, babbling or any positive affective vocalisations or utterances that signal engagement with the task and/or mother. AND/OR	- No display of interest/orientation towards mother or activity. OR - Engaged in activity with neutral affect. OR	- Facial expression such as frown, furrowed eyebrows, or vocalisation indicating distress, discomfort, sadness, protest, cry or fuss. - Infant startles due to mother's behaviour (e.g. mother's tone of voice too loud, mother shakes a rattle too close to infant's face) and

	Displays motor behaviour that signals engagement and/or excitement directed towards mother or activity (e.g. kicking legs, clapping hands, reaching or orienting towards mother)	Gaze is directed towards mother, toy or activity with no strong affect either positive or negative (e.g. holding toy, looking at mother with neutral facial expression)	not due to something extraneous to the interaction (e.g. doorbell ringing, interruption from sibling etc). - Infant deliberately avoids gaze or turns head to look away from mother or toy that she presents (not due to an engagement with something else). - Infant actively pushes away toy that mother presents (not due to an engagement with something else). - Infant displays motor behaviour/physical stance that indicates that he/she is uncomfortable (e.g. rigid arms, twisting body away from mother, arching back, pushing object away, pushing mother or mother's hand away)

12 Months	Positive Affect	Neutral Affect	Negative Affect
Mother	- Smiling, laughing or playful face (e.g. mock surprise, exaggerated emotional displays e.g pretend crying) directed towards infant. OR - Neutral <u>facial</u> affect accompanied by infant-directed speech (animated, high pitched tone) singing or noises directed at infant (e.g. kissing noises)	- Onset of a neutral facial expression AND/OR - Vocalising using a whisper (without obvious positive or negative facial affect) or a shushing or shhhhh sound. AND/OR - Mother is commenting on what is going on in a neutral tone.	Facial expression or vocalisation indicating sadness, anger, annoyance, irritation or sarcasm (e.g. saying positive or neutral words with a mocking tone)
Infant	Smiling, laughter, squealing, babbling or any positive affective vocalisations, utterances or words that signal engagement with the task and/or mother.	No display of interest/orientation towards mother or activity. OR	Facial expression such as frown, furrowed eyebrows, or vocalisation indicating distress, discomfort, sadness, protest, cry or fuss.

	AND/OR Displays motor behaviour that signals engagement and/or excitement directed towards mother or activity (e.g. clapping hands, reaching or orienting towards mother, directing mothers attention to something by either showing, pointing or vocalising towards it.)	OR - Engaged in activity with neutral affect. - Gaze is directed towards mother, toy or activity with no strong affect either positive or negative (e.g. holding toy, looking at mother with neutral facial expression)	- Infant startles due to mother's behaviour (e.g. mother's tone of voice too loud, mother shakes a rattle too close to infant's face) and not due to something extraneous to the interaction (e.g. doorbell ringing, interruption from sibling etc). - Infant actively pushes away toy that mother presents (not due to an engagement with something else). Infant displays motor behaviour/physical stance that indicates that he/she is uncomfortable (e.g. rigid arms, twisting away, arching back, moving body away from mother, pushing mother or mother's hand away, refusing to be held)