2012

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Recommended Citation
Glynn, LM (2012). Increasing parity is associated with cumulative effects on memory. *Journal of Women's Health, 21*, 1038-1048. DOI:10.1089/jwh.2011.3206

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JOURNAL OF WOMEN'S HEALTH
Volume 21, Number 10, 2012

DOI: 10.1089/jwh.2011.3206

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Abstract

Background: The purpose of this investigation was to determine if reproductive experience is associated with cumulative effects on human memory performance during pregnancy and if these effects persist into the postpartum period.
Methods: Verbal recall memory performance was assessed in 254 women four times during pregnancy and at 3 months postpartum. The relation between parity and memory function was evaluated with hierarchical linear modeling and analysis of covariance (ANCOVA).
Results: The data indicate that the previously documented adverse effects of pregnancy on memory performance are compounded with successive pregnancies. During gestation and postpartum, multiparity was associated with poorer memory function, and these effects did not appear to be due to differences in maternal demographics, depressive symptoms, or sleep quality.
Conclusions: Animal models demonstrate that the effects of reproduction on brain structure and function are both cumulative and enduring. However, little is known about the influence of reproductive experience on the human female brain. These findings provide evidence that in humans, reproduction is associated with striking and perhaps persisting changes in cognitive function.

Introduction

In the life span of the human female, no other naturally occurring hormone exposures are more extreme than those experienced during pregnancy, birth, and lactation. For example, during gestation, estradiol levels increase to 30 times greater than the peak during the menstrual cycle, and cortisol reaches levels similar to those in Cushing's syndrome and major melancholic depression.[1–3] A substantial literature exists indicating that less extreme endocrine events, such as puberty and menopause, which mark the onset and conclusion of the period in which the female is capable of reproduction, are associated with changes in both brain structure and function.[4,5] In contrast, almost nothing is known about how the hormone exposures linked to reproductive experience influence the brain and behavior of the human female. Work with rodent models has repeatedly demonstrated that alterations in cognitive performance and underlying neural systems emerge during pregnancy.[6–9] Further, these changes appear to be enduring in nature, a fact that is supported by two lines of evidence. First, parous rodents show alterations in cognitive function that persist throughout the life span. Specifically, females who have given birth display improved memory function that is present into old age, and they also appear to be protected from aging-associated neurodegeneration.[10–12] Second, some studies have shown that the effects of pregnancy are cumulative; that is, with successive litters and more mothering experience, the effects on function are greater. Multiparous females display enhanced cognitive function compared to primiparous and nulliparous females,[10,12] although not all studies demonstrate this effect.[13] Taken together, these findings suggest that parity imparts a lasting imprint on the brain and behavior of the female rodent. In light of these pervasive and long-term changes observed in nonhuman animals and the dramatic hormone exposures that characterize the prenatal endocrine milieu, it seems likely that pregnancy also exerts persisting influences on the human brain. In spite of this, a critical gap in our understanding of women's mental health exists. The nature of changes in brain and behavior that are affected by pregnancy and whether or not these alterations persist beyond parturition have yet to be determined.

In humans, a number of studies have shown that memory function declines during pregnancy, with the majority

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Table 1. Participant Characteristics

Characteristic	*Primiparous* (n = 113)	*Multiparous* (n = 141)	*t or Chi-square*	p *value*
Race/ethnicity (%)				
Latina	27	45	11.5	0.01
Non-Hispanic white	50	40		
Asian	13	6		
Other	10	9		
Maternal age (years)	27.9	30.3	−3.5	0.00
Education (%)			15.2	0.00
High school or less	17	17		
Associates or vocational degree	32	51		
4-year college degree	29	24		
Graduate degree	22	8		
Prenatal depression (CESD)	1.42	1.67	−1.1	0.26
Postpartum depression (EPDS)	5.0	5.6	−0.9	0.34
Prenatal sleep quality	5.4	5.6	−0.4	0.68
Postpartum sleep quality	6.2	7.2	−1.5	0.14

CESD, Center for Epidemiological Studies Depression Scale; EPDS, Edinburgh Postnatal Depression Scale.

detecting adverse influences on verbal recall memory (for a review and meta-analysis, see reference 14). In humans, the persistence of these effects is not well understood, however, because few studies have examined postpartum memory performance.[15–18] Two studies have compared function during gestation and postpartum to performance of women who were not pregnant. These suggest that diminished memory performance persists as late as 32 weeks postpartum.[17,18] Even less is known about the cumulative effects of repeated pregnancy experience in women. To date, no large study has examined the effects of parity on memory performance during pregnancy or the postpartum period. The one investigation of parity compared the performance of 22 primiparous and 26 multiparous women to the performance of nonpregnant women at a single point in gestation. The findings suggested that parity exerts additive effects on cognitive performance because the decrement in verbal recall memory performance was largest for the multiparous women.[19]

The purpose of the present longitudinal study is to further examine, in a large sample of women, if multiple pregnancies (increased parity) are associated with cumulative effects on memory function during pregnancy. Moreover, the enduring influence of reproductive experience will be assessed during the postpartum period. The study focused on verbal recall memory because the small body of existing literature suggests that this component of memory is most sensitive to the hormone exposures of pregnancy and also may differ depending on parity.[14,18] It was predicted that pregnant women who had given birth previously would exhibit the largest decrements in memory performance. It was further predicted that these cumulative effects of parity would persist at 3 months postpartum.

Materials and Methods

Participants

The 254 participants were selected from a large university medical center based on the following criteria: (1) singleton pregnancy, (2) over the age of 18, (3) English speaking, (4) nonsmoking, and (5) absence of any condition that could dysregulate neuroendocrine function. Participant characteristics are shown in Table 1.

Overview of study design

Pregnant participants were recruited by a research nurse during the first trimester of pregnancy. The women then participated in study visits at 14–16 (mean [M] 15.31, standard deviation [SD] 0.92), 24–26 (M 25.55, SD 0.93), 30–32 (M 30.96, SD 0.77), and 36+ weeks' gestation (M 36.7, SD 0.83) and also at 12–14 weeks postpartum (M 13.24, SD 1.08). At each visit, memory performance was assessed. The study was approved by the University of California Irvine Institutional Review Board, and all participants provided informed consent.

Dating of pregnancy and determination of pregnancy history

Prior pregnancy history was determined through medical interview and prenatal chart review conducted by a research nurse. Current pregnancies were dated according to current American College of Obstetricians and Gynecologists (ACOG) guidelines[20] by comparison of last menstrual period to estimates based on early ultrasound measurements by the research nurse at the first study visit at 15 weeks' gestation.

Memory assessment

Verbal recall memory was assessed with a paired-associates learning task. For this task, three sets of 12 unrelated word pairs were presented verbally. Immediately after presentation of each set of pairs, the participant was given the first word of each pair and was asked to supply the second word. The word pair lists were constructed from randomly chosen words that are five to eight letters long and that vary from 10 to 200 in frequency.[21] A paired-associate recall score was calculated by summing the number of correctly recalled words for the three sets of pairs.

Presentation of the five equivalent sets of stimulus materials was counterbalanced across participants. The memory assessment was conducted in a quiet, sound-attenuated room. Examiners were trained and directly supervised by a licensed

clinical psychologist. During each testing session, the examiners were videotaped, and randomly chosen sessions were reviewed by the research team to ensure consistency in administration of the memory assessment.

Potential covariates

In addition to maternal demographic information (race/ethnicity, education level, age) and lactation status, data were collected to assess both depressive symptoms and sleep quality for possible inclusion in statistical models.

Depressive symptoms. Depressive symptoms were assessed at each prenatal visit with the 9-item version of the Center for Epidemiological Studies-Depression scale (CESD).[22] Participants indicated whether they experienced a symptom (e.g., I felt depressed) from 0, rarely or none of the time, to 3, most or all of the time, during the last week, resulting in raw total scores between 0 and 27. Because validation analyses show that depression is best detected when individual items are rescored into a bivariate score,[22] each item was then scored 0 if option 0 or 1 was endorsed and was scored 1 if option 2 or 3 was endorsed. Bivariate scores ranged between 0 and 9, with a suggested cutoff score of ≥ 4. The 9-item scale has good internal consistency (K-R 20 = 0.87), and scores correlate highly with the original scale (r = 0.97). The average prenatal report of depressive symptoms for the study groups can be found in Table 1. The number of women who exceeded the cutoff for possible depression at each of the prenatal visits ranged from 7% to 12%. Parity was not associated with the probability of exceeding the clinical cutoff at any prenatal visit (chi-square < 0.66, $p > 0.42$).

At the postpartum visit, participants completed the 10-item Edinburgh Postnatal Depression Scale (EPDS),[23] a scale specifically developed to assess postpartum depression (PPD) (Table 1). Participants indicated how often they experienced a symptom in the past 7 days on a 4-point scale. Total scores varied between 0 and 30. At the postpartum visit, 16% of the women scored above the cutoff for probable depression (>10). The proportion of women scoring above the cutoff was not associated with parity (chi-square 0.10, $p = 0.76$). The scale has good reliability (split-half: 0.88, standardized α: 0.87).

Sleep quality. The Pittsburgh Sleep Quality Index (PSQI),[24] an 18-item questionnaire, was used to measure habitual sleep quality over the previous month. It comprises seven subscales assessing habitual duration of sleep, nocturnal sleep disturbances, sleep latency, sleep quality, daytime dysfunction, sleep medication use, and sleep efficiency. Each subscale has a possible score of 0–3, with an overall global score of 0–21. Higher scores reflect poorer sleep quality. The PSQI and its psychometric properties have been validated in pregnant women.[25–27] The questionnaire was given at each prenatal study visit and also at the postpartum visit. This questionnaire was introduced after study commencement, so sleep data were available for 140 of the participants. Mean sleep quality (prenatal average and postpartum) for the study groups can be seen in Table 1.

Data analysis strategy

Memory performance across gestation was assessed with multilevel modeling using hierarchical linear modeling (HLM) growth curve analysis [28] with HLM software (Scientific Software International). This technique allows for determination of between-person differences (parity) in within-person trajectories (change in memory performance during pregnancy). HLM offers several advantages over other Ordinary Least Squares statistical methods for evaluation of variation over time. First, standard regression or analysis of variance (ANOVA) models are limited to one component of variability, the deviation of the individual from the group mean. In comparison, HLM also takes into account the within-person variability assessed over time. Second, estimates of the lack of fit in modeling each individual's data are derived, and the less reliable data are weighted less heavily. Third, HLM produces robust estimates despite missing values for the repeated dependent measure. Cases with complete data are weighted more heavily, but all cases are included in the estimation of effects

A two-level model was used to assess the effects of parity on verbal recall memory. In the full model, the effects of parity and demographic covariates on memory performance at the initial visit (14 weeks) and linear change across time were evaluated. Specifically, the level 1 variables (or the time-variant variables) included memory performance across the prenatal assessments and gestational week at assessment. Thirteen percent of the women were missing data at one of the four prenatal visits, and an additional 6 % were missing data from two of the visits. The remaining participants had complete data for each prenatal visit. The level 2 variables (or time-invariant variables) included parity (0 or 1+; entered as a dichotomous variable) and demographic covariates. The full model was then repeated at the group level for each gestational week between the first study visit at 15 weeks' until the last assessment at 39 weeks' gestation. A linear model was constructed because preliminary testing indicated that the addition of quadratic and cubic components did not improve the predictive values of the model. The level 1 model was statistically significant and indicated that memory performance improved slightly across assessments. To further explore the cumulative effects of parity on memory performance during pregnancy, these HLM analyses were repeated entering parity as a continuous level 2 predictor (range 0–4).

Differences in postpartum memory performance were assessed with a one-way analysis of covariance (ANCOVA) with parity as the predictor (parity groups, 0 vs. 1+). The covariates included are described below. The postpartum ANCOVA model was repeated with expanded parity groups (parity groups: 1, 2, and 3 or more) to further determine the additive effects of pregnancy on memory performance.

The following factors were considered as potential covariates: race/ethnicity, education level, maternal age, depressive symptoms, sleep quality, and lactation status (at the postpartum visit). Race/ethnicity, education level, and maternal age each were associated with both parity and memory performance (at the $p < 0.05$ level), and these were included in all analyses of memory performance (i.e., HLM and ANCOVA). In addition, lactation status also was related to both predictor and outcome and was included as a covariate in the postpartum analyses.

Results

Comparison of primiparous to multiparous women

Beginning at 16 weeks' gestation (but not before), the performance of the women who had previously given birth was

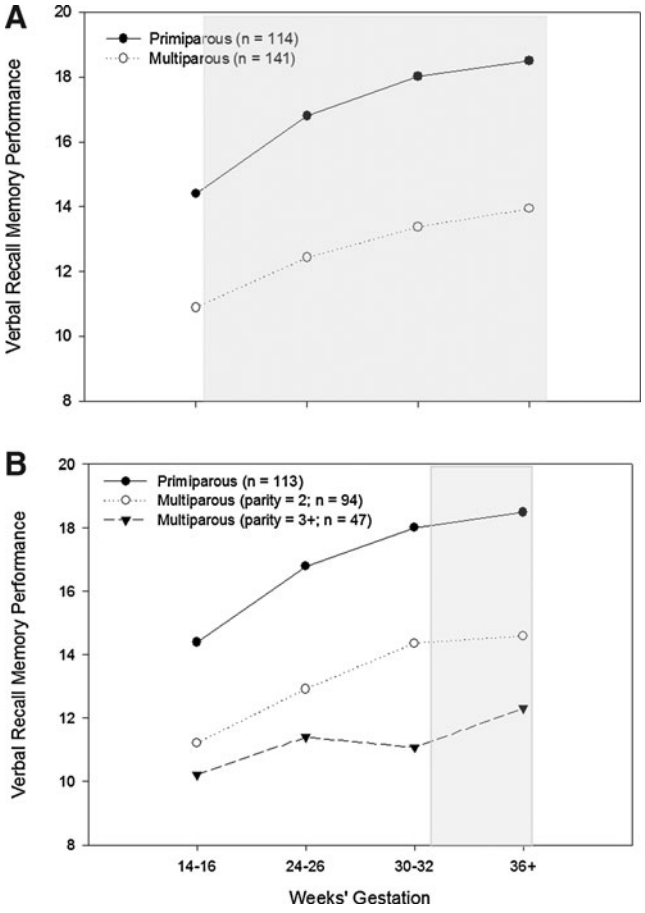

FIG. 1. **(A)** Verbal memory performance across gestation for primiparous and multiparous women. Hierarchical linear modeling (HLM) analyses revealed that from 16 weeks' until the last study visit at 39 weeks' gestation, performance was poorer among multiparous women compared to primiparous women (statistically significant group differences are indicated by the shaded areas). **(B)** Verbal memory performance during gestation for women of varying levels of parity (1, 2, and 3+). HLM analyses with parity analyzed as a continuous variable revealed cumulative effects of parity. The contributions of race/ethnicity, maternal age, and education level were included in all HLM models. The increase in performance across gestation for all parity groups can be attributed to the expected effects of repeated administration (i.e., practice effects).

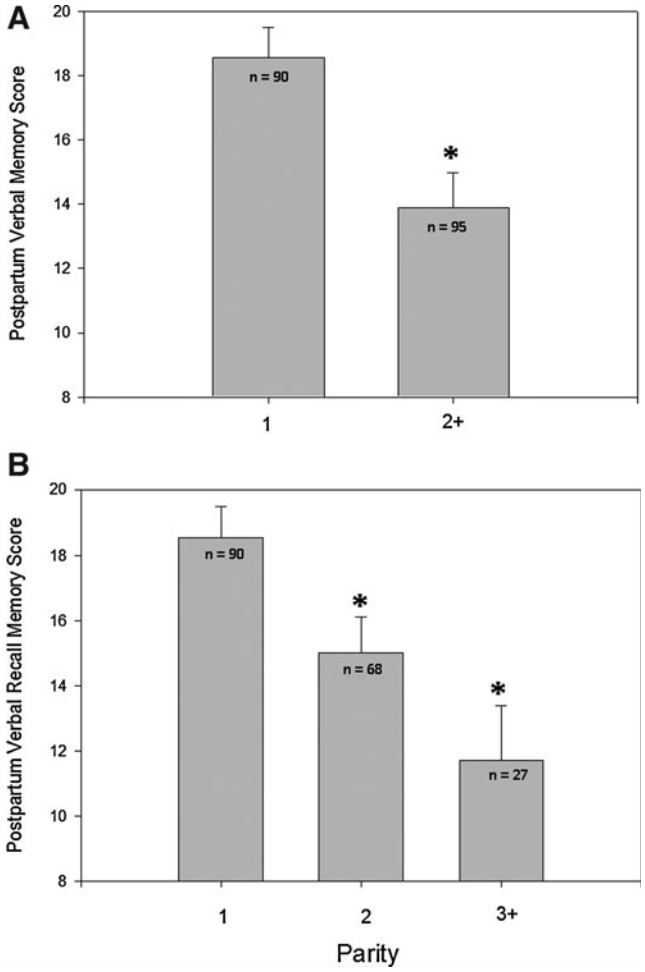

FIG. 2. **(A)** At 3 months postpartum, primiparous women were exhibiting better verbal recall memory compared to multiparous women. **(B)** Persisting and cumulative effects of parity on memory performance. During the postpartum period, higher parity was associated with poorer memory function, and the effects appear to be additive.

poorer than the performance of those who had not (Fig. 1A). The performance of the primiparous women exceeded that of the multiparous women at each gestational week beginning at 16 weeks' gestation until the last assessment at 39 weeks' (Bs range -2.1 to -2.8, $p < 0.05$).

The effects of parity on memory performance were still present at 3 months postpartum (Fig. 2A). Primiparous women were exhibiting better performance than multiparous women (one-way ANCOVA: $F(1,179) = 5.45$, $p < 0.05$).

Further analysis of cumulative effects of parity

The first set of analyses revealed that those women who were giving birth for the first time showed better memory performance during pregnancy and in the postpartum period than the women who had experienced at least one prior pregnancy. However, these analyses did not test whether or not reproductive experience exerts additive or cumulative effects beyond those of the first pregnancy. Repeating the analyses of prenatal memory performance with parity assessed as a level 2 continuous variable confirmed that reproductive experience exerts cumulative effects during gestation. Specifically, from 34 weeks' until the last assessment at 39 weeks', each additional previous pregnancy was associated with poorer performance (Bs range -1.1–-1.4, $p < 0.05$) (Fig. 1B).

At 3 months postpartum, performance was consistent with cumulative effects of pregnancy on memory, with the primiparous women exhibiting the best performance (parity = 1), those who had given birth twice performing the next best (parity = 2), and those who had given birth three or more times performing the most poorly (parity 3+) (2, 178) = 2.82, $p = 0.06$) (Fig. 2B).

Discussion

The current study indicates that the adverse effects of pregnancy on human verbal recall memory performance are

compounded with successive pregnancies. During gestation and at 3 months postpartum, increased parity was associated with poorer memory function. These findings are consistent with the single other human study that compared memory performance of primiparous to multiparous women once during pregnancy[19] and indicate, for the first time in humans, that the effects of repeated reproductive experience on memory performance persist into the postpartum period. These data raise the important question of whether or not these cumulative changes are very long-lasting or even permanent. Animal models have demonstrated that the effects of reproduction and mothering on cognitive function and brain structure are additive and persist throughout the life span.[6,12] More broadly, the findings provide additional evidence that as with rodent mothers, in human mothers, reproduction is associated with striking and pervasive neural plasticity.

Studies in humans consistently demonstrate that verbal memory, as opposed to other components of memory, is most sensitive to reproductive experience.[14,18] It is not yet known if this alteration is of adaptive significance or is merely a by-product of the prenatal conditions necessary to generate the onset of optimal maternal behaviors.[29] There is some evidence from the rodent model that suggests memory decrements may represent the cost of the architectural remodeling of the maternal brain. The long-term consequences of reproductive experience in the rat dam include enhanced cognitive function and less aging-related neurodegeneration.[10] However, close examination of the timing of these changes reveals a temporary decrement in cognitive performance, which precedes the enhancements. During the postpartum period before weaning, rodent mothers show a reduction in memory function,[8,9] which then is followed by improvements in memory function across the rest of the life span.[6] Further, at least one study has shown that the quality of maternal behavior is inversely associated with mothers' reference memory.[30] That is, those dams that spend the most time licking and grooming their pups show the poorest memory function during the preweaning period. No longitudinal study in humans has followed women postpartum farther than 32 weeks, and at that point, the decrement in memory performance still is present.[17] Whether or not these decrements persist or, more intriguingly, whether over the longer term the parous women exhibit enhanced cognitive abilities and perhaps even protection from neurodegeneration represents a critical agenda for understanding women's mental health.

The endocrine mechanisms underlying pregnancy-induced changes in human memory function remain to be fully elucidated, but there is considerable agreement about the potential role of alterations in gonadal and adrenal hormones.[31,32] During the third trimester of pregnancy, levels of estradiol are 30 times greater than levels during the peak of the menstrual cycle,[33] and cortisol reaches levels consistent with those seen in Cushing's syndrome and major melancholic depression.[2,34,35] Both glucocortioids and estrogens affect memory function in the nonpregnant state,[36,37] rendering it highly likely that the more extreme changes in these hormones during gestation also are associated with alterations in function. Recently, the first study in humans has provided support for an endocrine basis of the memory changes during and after gestation. Specifically, prenatal estradiol and cortisol trajectories were linked to decrements in recall memory performance during gestation and during the postpartum period.[18]

The changes in memory function, such as those seen here, probably reflect both underlying structural and functional changes in the brain. To date, two studies have assessed the structural changes in the brains of women who have given birth. The first demonstrated that overall brain size during pregnancy is smaller relative to the postpartum period.[38] More recently, Kim et al.[39] reported increased gray matter volumes in the prefrontal cortex, parietal lobes, and midbrain areas at 3–4 months compared to 2–4 weeks postpartum. Despite the paucity of evidence, the existence of specific parity-related neurologic changes in humans is highly plausible because acute fluctuations in estrogens of a more modest scale are associated with both structural and functional alterations. For example, hormone changes associated with the menstrual cycle are associated with alterations in gray matter density in the hippocampus[40] and also with changes in orbitofrontal cortex activity in response to emotional stimuli.[41]

The plausibility of neurologic change in the human maternal brain is further increased by work with animal models. In rodents, parity is associated with increased estrogen receptor protein expression in the medial preoptic area (mPOA) and the amygdala[42] and with enhanced long-term potentiation (LTP) both N-methyl-D-aspartate (NMDA) and non-NMDA receptor mediated) in the hippocampus.[11,43] Further, multiparity is associated with increased cell body size and number and length of dendritic branches in the mPOA,[44] increased hippocampal dendritic spine densities,[45,46] and increased cell proliferation in the forebrain subventricular zone.[47]

The strengths of this study include the large sample size, the carefully characterized sample, and its longitudinal design. Because this study relied on naturally occurring differences in parity rather than experimental manipulation, it is not possible to draw causal conclusions. However, the statistical models employed did adjust for the effects of critical demographic characteristics, including race/ethnicity, maternal age, and education level, and these did not account for the effects of parity on memory. Further, neither depressive symptoms nor sleep quality were related to parity and cannot account for the findings. Confidence in these findings is increased for two additional reasons. First, prenatal hormone trajectories predict the magnitude of the changes in memory function during gestation.[18] Second, some animal models, for which random assignment to number of litters is possible, have demonstrated cumulative effects of reproductive experience on brain and behavior.[10,12]

The present study focused on verbal recall memory because the small existing body of literature examining memory changes in human pregnancy suggests that this may be the component of memory most sensitive to the physiologic changes of pregnancy.[18] The findings confirm women's common anecdotal reports of impaired memory during pregnancy[48,49] and represent an important piece of information for further understanding the relation between reproductive history and cognitive function in the human mother. However, this investigation represents a single step in the larger framework necessary to characterize the influences of reproductive history on the human maternal brain and behavior. To provide a comprehensive understanding, there are several critical directions for future research. First, the range of cognitive functions and behaviors under examination must

be expanded. In the realm of cognition, a potentially fruitful pathway would be to investigate cognitive functions more directly relevant to caring for a new infant. Taking a broader evolutionary perspective, verbal recall memory, which is compromised during and after pregnancy, is a relatively recent adaptation and while essential for performing in the modern workplace, for example, it is likely to be less central to success in caring for an infant. However, such skills as attention to infant cues, the ability to multitask (or divide attention), and the ability to detect threat might be enhanced by pregnancy and child rearing.

Two existing studies provide evidence for improved cognitive function, reporting that among human mothers, the ability to recognize emotions and to detect infant distress are enhanced,[50,51] skills that might be critical for responsive mothering and for detection of threats to one's offspring. Outside the domain of cognitive function, careful longitudinal studies are necessary to assess alterations in stress responding. During human pregnancy, both physiological and psychological responses to stress are dampened.[52–55] Stress responding is similarly affected across a range of other nonhuman species.[56,57] It is plausible that a higher threshold for inducing a stress response among mothers is advantageous for defending young from environmental threats. A second broad direction for continued work relates to understanding the persistence of the alterations related to pregnancy and mothering. In rodent dams, many of the effects on stress responding and cognitive function are still present at the end of the life span.[10–12] The persistence of these effects on the human maternal brain and behavior has yet to be examined and is likely to have important implications for life span health and development, including cognitive aging. Last, although across many species the hormone exposures of pregnancy are necessary for optimal initiation of maternal behaviors,[58,59] clearly this is but one stage of the maternal programming process. The last broad direction to guide future research involves creating comprehensive models of maternal programming that incorporate life history (e.g., the quality of maternal care the mother herself received), gestation, delivery, lactation, weaning, and exposure to and interaction with offspring.

It has been proposed that the development of maternal behaviors represents one of the primary forces shaping the evolution of the mammalian brain.[60,61] It also is clear that within the female's lifetime, the hormone exposures during pregnancy, birth, and lactation are critical determinants of the onset and maintenance of sensitive and responsive maternal behavior.[58,59] Several of the hormones that are associated with the memory decrements seen in the present study also play an integral role in initiation of maternal behaviors.[62–66] It appears increasingly probable that the hormone exposures necessary for restructuring of the maternal brain to optimize maternal care giving also may be associated with costs. Human pregnancy has been linked to diminished function on some tasks (e.g., verbal recall memory as in the present study) and also to enhancements on others (recognition of emotion and infant distress[50,51]). The vast majority of women give birth to at least one child, and a result, a significant proportion of the adult population in the United States has their neurologic abilities and functions distinctly altered by the transient state of pregnancy. Understanding the antecedents and consequences of the pregnancy-associated changes in the human brain and behavior is of vital importance to allow clinicians to provide informed and comprehensive care to the 85% of women who experience pregnancy and childbirth.

Acknowledgments

The author thanks the families who participated in this project, Cheryl Crippen and Carol Holliday for their excellent work, and Curt Sandman, Elysia Davis, and the anonymous reviewers for thoughtful editorial feedback. This work was supported by USPHS HD-40967.

Disclosure Statement

The author has no conflicts of interest to report.

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