NIH Public Access
Author Manuscript
Sci Signal. Author manuscript; available in PMC 2013 November 22.

Published in final edited form as:
Sci Signal. ; 5(245): . doi:10.1126/scisignal.2003406.

Fetal Programming of Brain Development: Intrauterine Stress and Susceptibility to Psychopathology

Claudia Buss[1,5,*], **Sonja Entringer**[1,5], and **Pathik D. Wadhwa**[1,2,3,4,5]

[1]Department of Pediatrics, University of California, Irvine, School of Medicine, Irvine, CA 92697, USA.

[2]Department of Psychiatry and Human Behavior, University of California, Irvine, School of Medicine, Irvine, CA 92697, USA.

[3]Department of Obstetrics and Gynecology, University of California, Irvine, School of Medicine, Irvine, CA 92697, USA.

[4]Department of Epidemiology, University of California, Irvine, School of Medicine, Irvine, CA 92697, USA.

[5]University of California Irvine Development, Health and Disease Research Program, University of California, Irvine, School of Medicine, Irvine, CA 92697, USA.

Abstract

The fetal brain is highly plastic and is not only receptive to but requires cues from its environment to develop properly. Based on an understanding of evolutionary biology, developmental plasticity, and life history theory, one can predict that stressors are an important environmental condition that may influence brain development. In fact, the available empirical evidence appears to support the notion that exposure to excess stress in intrauterine life has the potential to adversely affect short- and long-term neurodevelopmental outcomes with implications for altered susceptibility for mental health disorders in childhood and adult life. In this presentation, we provide a rationale for proposing that endocrine and inflammatory stress mediators are key candidate pathways for programming brain development. These mediators are responsive to a diverse set of intrauterine perturbations and alter key signaling pathways critical for brain development, including but not limited to mammalian target of rapamycin, Wnt (wingless), Sonic hedgehog, and reelin signaling. We suggest that recent advances in neuroimaging and other methods now afford us an unprecedented opportunity to advance our understanding of this important topic. Additionally, we provide empirical evidence from two recently published papers for fetal programming of human brain development. We conclude by suggesting some future directions for expanding this field of research.

Copyright 2008 by the American Association for the Advancement of Science; all rights reserved.

[*]**Presenter and corresponding author**. cbuss@uci.edu.

A Presentation from the European Society for Paediatric Endocrinology (ESPE) New Inroads to Child Health (NICHe) Conference on Stress Response and Child Health in Heraklion, Crete, Greece, 18 to 20 May 2012.

This contribution is not intended to be equivalent to an original research paper. Note, in particular, that the text and associated slides have not been peer-reviewed.

NIH-PA Author Manuscript
NIH-PA Author Manuscript
NIH-PA Author Manuscript

NIH-PA Author Manuscript

NIH-PA Author Manuscript

NIH-PA Author Manuscript

Presentation Notes

Slide 1: *Science Signaling* logo

The slideshow and notes for this presentation are provided by *Science Signaling* (http://www.sciencesignaling.org).

Slide 2: Title page

Within the context of the larger issue of fetal programming of brain development, this Presentation focuses on the putative role of intrauterine stress and stress biology in altering susceptibility for subsequent psychopathology.

Slide 3: Outline

First, we will outline the rationale for establishing and appreciating the importance of the intrauterine environment in programming brain development. Specific issues and considerations will be discussed, including why the brain is a particularly prominent target for fetal programming, why intrauterine stress and stress biology are likely candidate processes for shaping the developmental trajectory of the brain, how (through which signaling pathways) these biological mediators can affect the developing brain, and various approaches for the study of fetal programming of human brain development. Next, we will present empirical evidence for fetal programming of human brain development from recently published papers. Finally, this Presentation will conclude by suggesting future directions for expanding this field of research.

Slide 4: Conceptual framework— The traditional view

Alterations in brain anatomy and structural and functional connectivity have been associated with several neurodevelopmental and neuropsychiatric disorders (1, 2). Many of these alterations in the brain are believed to precede disease onset and be causally related to disease symptoms and severity (vulnerability hypothesis) (3). This raises the question of what may cause these early alterations in the brain. Based on measures of putative genetic influence, such as heritability and recurrence risk ratios, the current and dominant research paradigm in the field postulates a major genetic contribution for common neuropsychiatric disorders. However, efforts to identify risk-conferring alleles have largely been unfulfilled (4). It seems unlikely that variation in the genetic makeup alone can meaningfully explain differences in the detailed neural architecture of the brain: It is highly unlikely that less than 30,000 genes can determine the connectivity of all 240 trillion synapses in the cerebral cortex. ADHD, attention deficit hyperactivity disorder.

Slide 5: Fetal programming of brain development

The traditional view is rapidly being replaced by a model that considers the interplay between genes and the early environment in directing development. Whereas brain development may start from a so-called genetic blueprint, it is the overlay of experience onto this blueprint that shapes development and leads to either normal structure and function or altered susceptibility for psychopathology. Therefore, conditions during early development are likely to play an important role in this process (5). Fetal programming describes the process by which conditions during critical periods of cellular proliferation, differentiation, and maturation and the developing organism's response to these conditions elicits structural and functional changes in cells, tissues, and organ systems that may have long-term or permanent consequences (6, 7). Thus, brain development is a product of the dynamic, bidirectional interplay between the individual's genotype, acquired at conception, and the nature of the early environment, extending from embryonic and fetal life through birth, infancy, and into childhood and beyond. CRH, corticotrophin-releasing hormone

NIH-PA Author Manuscript

NIH-PA Author Manuscript

NIH-PA Author Manuscript

Slide 6: Issues and questions

The fetal programming concept raises the following issues and questions, which are addressed in the next few slides: (i) Which organ systems are particularly susceptible to environmental influences during development? (ii) During which periods of development are the influences of environmental conditions particularly pronounced? (iii) Which particular environmental conditions exert the largest influence on development or represent the most potent programming cues? (iv) How, or through which pathways, do stress-related environmental conditions influence brain development? (v) What approaches can be used to study fetal programming of brain development?

Slide 7: Which organ systems are particularly susceptible to environmental influences during development?

The ontogeny of brain development is considerably longer than that of other organ systems. Brain development extends from the fetal period of life into the neonatal, infant, childhood, and adolescent years. No other organ system remains as plastic and continues to develop over such a prolonged period. Given that one of the principles of developmental programming is that organs undergoing rapid developmental changes are especially vulnerable to the influences of environmental conditions, the brain is a prominent target for such influences. The fetal developmental period is particularly important, because this is the stage at which growth and differentiation of major brain structures occur. Because brain development involves a cascade of bidirectional interactions with the environment, even small or subtle alterations in brain structure or function during fetal life can become progressively and substantially magnified over time to produce long-lasting or permanent deficits.

Slide 8: During which periods of development are the influences of environmental conditions particularly pronounced?

We suggest that the prenatal period is the developmental interval that is most sensitive to the influence of environmental factors. In a seminal paper published in 2011, Kang *et al.* took a large number of postmortem human brains (ranging in age from 5.7 weeks postconception to 82 years) and analyzed the spatiotemporal changes in gene expression that occur in all of the major brain areas (8). Kang *et al.* found that 90% of the genes they analyzed were expressed differently across brain regions or over time, or both, and that the majority of these spatiotemporal differences occurred before birth. After birth, the regional transcriptomes of the different brain areas became more similar. These three figures taken from (8) present expression patterns of genes involved in cell proliferation (black), cell differentiation and migration (green), synapse development (red), dendrite development (blue), and myelination (yellow) in three different regions of the brain: the neocortex (NCX), the hippocampus (HIP), and the cerebellum (CBC). These results demonstrate that dynamic changes in gene expression are a feature of the prenatal period of brain development.

Slide 9: Which particular environmental conditions exert the largest influence on development?

The rationale for considering a role for stress and stress biology in fetal programming of brain development derives, in part, from concepts in evolutionary biology, developmental plasticity, and life history theory. From conception onward, the fetus and the mother both play an obligatory, active role in all aspects of development. Based on the consideration that key environmental conditions that have shaped natural selection and developmental plasticity include not only variation in energy substrate availability (nutrition) but also challenges that have the potential to affect the structural or functional integrity and survival of the organism (stress), it is likely and plausible that prenatal stress and stress biology

NIH-PA Author Manuscript

NIH-PA Author Manuscript

NIH-PA Author Manuscript

represent an important aspect of the intrauterine environment that would be expected to influence many, if not all, neurodevelopmental outcomes (9, 10).

Slide 10: How, or through which pathways, do stress-related environmental conditions influence brain development?

We suggest that the major pathways through which non-nutritional environmental factors affect brain development include stress-related maternal-placental-fetal endocrine and inflammatory pathways. These processes play a critical, obligatory role in neuronal and glial cell migration, cellular differentiation, synaptic maturation, and other important aspects of brain development. Several studies have demonstrated that fetal exposure to excessive amounts of stress can interfere with normal brain development and result in detrimental effects (11). These neurodevelopmental consequences of exposure to elevated concentrations of endocrine and inflammatory stress mediators in animals include changes in cell proliferation, neuronal differentiation and gliogenesis (12–14), cell survival (15), synaptogenesis (16), myelination (17–20), and adult neurogenesis (21), as well as changes in the availability of key mediators such as neurotrophic factors (22), neurotransmitters (23), growth factors (24), and thyroid hormones (25–27). Stress-related endocrine and inflammatory markers may serve as signals for a wide range of maternal, placental, or fetal stressors, including but not limited to nutrient availability, oxygen availability, the presence of obstetric complications such as preeclampsia and infection, and other important environmental conditions that can sculpt brain development and alter the neurophenotype (28). For these reasons, these endocrine and inflammatory biological measures are considered summary indicators of a diverse range of adverse intrauterine conditions (9, 29). IL-6, interleukin-6; TNF-α, tumor necrosis factor–α.

Slide 11: What are the key signaling pathways by which stress-related endocrine and inflammatory pathways influence brain development?

We suggest that stress-related endocrine and inflammatory mediators may influence brain development directly by affecting the key signaling pathways implicated in this process and indirectly by altering the availability or actions of major neurotrophic factors, neurotransmitters, growth factors, and thyroid hormones. This slide lists the key signaling pathways that are critically involved in brain developmental processes and, therefore, are candidates for mediating the effects of stress factors. First is the mammalian target of rapamycin (mTOR) signaling pathway: mTOR is a serine-threonine protein kinase that integrates input from upstream pathways to regulate cell growth and survival, protein synthesis, and transcription. Second is the Wnt signaling pathway: Wnt ligands are morphogens that influence cell-fate decisions and tissue patterning. The third is the Sonic hedgehog (Shh) pathway: Shh and homologous proteins play crucial roles in cell-fate determination and differentiation along the dorsoventral axis of the developing neural tube. Finally, reelin signaling is also likely to be an important mediator of stress factors. Reelin is an extracellular matrix glycoprotein involved in regulating processes of neuronal migration and positioning in the developing brain.

Slide 12: Key signaling pathways— Glucocorticoids and mTOR, Wnt, Shh, and reelin signaling

Glucocorticoids are the major stress-related endocrine ligands in mammals. Exposure to inappropriate concentrations of glucocorticoids can alter the brain developmental trajectory through their actions on key signaling pathways. For example, high concentrations of glucocorticoids inhibit mTOR signaling, as evidenced by decreases in the levels of phosphorylated p70 ribosomal S6 kinase (p70S6K) and its target, ribosomal protein S6 (30). The synthetic glucocorticoid dexamethasone induces an up-regulation of the Wnt antagonist Dickkopf 1, thereby markedly decreasing proliferation and neuronal differentiation while

NIH-PA Author Manuscript

NIH-PA Author Manuscript

NIH-PA Author Manuscript

promoting glial cell formation (13). High concentrations of glucocorticoids suppress Shhinduced proliferation of neural progenitor cells. Conversely, Shh signaling protects against glucocorticoid-induced neonatal brain injury by inducing production of the enzyme 11 β-hydroxysteroid dehydrogenase type 2 (11β-HSD2), which catalyzes the conversion from active cortisol to inactive cortisone (31). Chronic exposure to corticosterones such as glucocorticoids is associated with a decrease in the number of reelin-positive cells (32).

Slide 13: Key signaling pathways— Neurotrophic factors

Neurotrophic factors promote neurodevelopmental processes such as neuronal differentiation, survival, and growth, as well as synaptic plasticity (33). Biological stress mediators can alter the availability of neurotrophic factors. For example, dexamethasone inhibits the brain-derived neurotrophic factor (BDNF)–dependent up-regulation of dendritic outgrowth and production of synaptic proteins (34).

Slide 14: Key signaling pathways— 5-HT

Serotonin (5-HT) can affect neural cell migration by altering reelin signaling (35), accelerate axon growth by increasing cyclic adenosine monophosphate (cAMP) and subsequent opening of cAMP-gated sodium channels (36), and affect synaptogenesis by activating the Rho family small guanosine triphosphatase (GTPase) Cdc42 through phospholipase C and phosphoinositide 3-kinase (PI3K) pathways (37). Endocrine and immune stress mediators have been shown to reduce serotonin availability and may thus impair brain developmental processes such as cell migration, axon development, and synaptogenesis (38, 39).

Slide 15: Key signaling pathways— Growth hormones

Growth hormone signaling plays an important role in cell proliferation and axon development by activating the mitogen-activated protein kinase (MAPK) signaling pathway (40) and also exerts anti-apoptotic effects through the PI3K-Akt pathway and MAPK-ERK (extracellular signal–regulated kinase) signaling pathway (41). High concentrations of glucocorticoids have been shown to reduce growth hormone production (24) and may therefore affect cell proliferation and survival and axon development by interfering with these pathways.

Slide 16: Key signaling pathways— Thyroid hormones

Thyroid hormone (TH) signaling plays an important role in cell migration by activating reelin signaling (42), in differentiation of embryonic neural stem cells (promotion of neural proliferation and inhibition of astrocyte differentiation) by inhibiting signal transducer and activator of transcription 3 (STAT3) signaling through TH receptor alpha 1 (TRα1) (43), and in cell proliferation and differentiation by activating Shh signaling (44). Inhibition of thyroid hormone production by cortisol (25) or by the proinflammatory cytokines IL-6 (26) and TNF-α (27) may interfere with these pathways to affect neuronal migration, proliferation, and differentiation.

Slide 17: Approaches to study fetal programming of brain development— Animal models

Most of what is known about fetal programming of the brain stems from animal studies, mainly rodent and a few nonhuman primate studies. The complexity of brain anatomy and connectivity varies greatly between species. Furthermore, the magnitude of the impact of environmental conditions on brain development also differs between species. Compared with larger species, smaller species exhibit an accelerated trajectory of brain development, which results in amplified consequences of environmental influences. Also, there is considerable variation in the developmental ontogeny of the various components of brain development across species: Some mammals, such as rodents, exhibit a more mature brain at

NIH-PA Author Manuscript

NIH-PA Author Manuscript

NIH-PA Author Manuscript

birth than other mammals, implying that brain maturation occurring in the early postnatal period in one species (for example, rat) takes place in late gestation in other species (e.g., humans) (45). Thus, although the contributions from animal studies have been extremely valuable, they do not necessarily extrapolate directly to the human brain.

Slide 18: Approaches to study fetal programming of brain development— Structure-function relationships

Brain anatomy and connectivity underlie brain function and, therefore, behavior. But the converse also holds true: Behavior, or function, also affects the anatomy and wiring of the brain. This has been demonstrated, for example, in the context of environmental enrichment or physical activity– related changes in the anatomy of the brain (46, 47). Cross-sectional assessments of brain structure (neuroimaging) and function (behavioral assessments) are limited in their ability to elucidate the temporal sequence of structure-function relationships. Longitudinal brain imaging studies with serial assessments of structure and function will be required to untangle these relationships. When using imaging-based approaches that quantify variation in brain structures, it may be difficult to interpret the underlying reason(s) for observed differences. For instance, a smaller volume of a particular brain structure could be a result of permanent neuronal loss or reversible deficits in more plastic characteristics such as dendritic length and branching. Hence, complementary mechanistic studies in animal models are warranted. MRI, magnetic resonance imaging.

Slide 19: Empirical evidence for fetal programming of human brain development

We present here two examples from recently published studies (48, 49). In the first study, the association was assessed between variation in maternal concentrations of the stress hormone cortisol during pregnancy and subsequent measures of child brain development. In the second study, the association was assessed between a clinical condition associated with a high maternal inflammatory milieu (maternal obesity) and subsequent measures of child brain development.

Slide 20: Study overview

The findings discussed in these two examples stem from a prospective, longitudinal study of mothers and their children that incorporated up to five maternal psychosocial and neuroendocrine assessments during pregnancy and subsequent child neurocognitive assessments between 6 and 9 years of age. In both studies, the effects of the following potential confounding variables were statistically controlled: obstetric complications; gestational age at birth; birth weight; maternal postnatal depression; and intelligence quotient (IQ), race, ethnicity, age, and sex of the child. PC, pre-conception; P, puberty.

Slide 21: Study I—Maternal cortisol and child brain development

Cortisol, the end product of the hypothalamic-pituitary-adrenal (HPA) axis, exerts a wide array of metabolic, endocrine, and immune effects (50, 51) and plays a key role in events underlying the development of the brain (52). Cortisol is one of the primary biomarkers of physiological stress because its production, bioavailability, and activity are altered by all adverse conditions that have been shown to affect the developing brain (29). Thus, although glucocorticoids play an essential role in normal brain development, abnormal or inappropriate concentrations, particularly during sensitive periods, may cause neurotoxicity with detrimental long-term consequences (53).

NIH-PA Author Manuscript

NIH-PA Author Manuscript

NIH-PA Author Manuscript

Slide 22: Prenatal cortisol concentrations, limbic structures, and affective problems in the child

We examined the association between endogenous maternal cortisol concentrations during pregnancy and the volumes of the child amygdala and hippocampus (assessed by manual segmentation of structural magnetic resonance images), as well as affective problems in the child [assessed with the Child Behavior Checklist (CBCL)] (54). The CBCL affective problem scale reflects symptomatology characteristic of dysthymia and major depressive disorders. These analyses controlled for all of the covariates listed previously (slide 20). N = 65 patients.

Slide 23: Communication between mother and fetus

Implicit in this study is the premise that during pregnancy cortisol concentrations in the maternal compartment are an indicator of fetal glucocorticoid exposure. This idea is supported by several plausible pathways, as summarized in the figure. Direct fetal exposure to maternal cortisol is regulated by the placental enzyme, 11β-HSD2, which oxidizes cortisol to its inactive form, cortisone (55, 56). Because placental 11β-HSD2 serves only as a partial barrier, some proportion of active maternal cortisol does pass through the placenta into the fetal compartment (57). Interestingly, many adverse intrauterine conditions that have been associated with impaired fetal brain development have also been linked to a down-regulation of placental 11β-HSD2 activity, including high maternal anxiety (58), severe infection (59), increased abundance of proinflammatory cytokines (60), and alcohol exposure (61). Another pathway by which maternal cortisol could produce elevations in fetal cortisol is by stimulating and thereby increasing the production of placental CRH (62–64), which is known to act on the fetal HPA axis and stimulate adrenal steroid biosynthesis in the fetus. ACTH, adrenocorticotropic hormone.

Slide 24: Results I

High maternal cortisol concentrations in early but not later gestation are associated with larger right amygdala volumes in girls, but not boys. The magnetic resonance images shown on this slide depict the segmented left (blue) and right hippocampus (green), as well as the left (pink) and right (red) amygdala in the sagittal, coronal, and horizontal views (from left to right). The upper left graph shows cortisol concentrations over the course of gestation in mothers of girls, who, at 7 years of age, have a large right amygdala volume (blue), versus in mothers of girls, who, at age 7, have a small right amygdala volume (yellow). Higher levels of maternal cortisol at 15 weeks gestation are associated with larger right amygdala volumes in girls (also depicted in the scatter plot in the upper left inset). The graph on the upper right shows maternal cortisol concentrations over the course of gestation in mother of boys in dependence of their right amygdala volumes. At no time point during gestation were maternal cortisol concentrations associated with the size of the right amygdala in 7-year-old boys. Maternal cortisol concentrations were not associated with the size of the left amygdala or the left or right hippocampus in either girls or boys, which is not shown on this slide (48).

Slide 25: Results II

Mediation analyses show that the association between high maternal cortisol concentrations and higher prevalence of child affective problems is partially mediated by the larger amygdala volumes.

Slide 26: Maternal prenatal cortisol and child limbic structures

The results of this study suggest greater susceptibility of the developing brain to high maternal prenatal cortisol concentrations in female versus male fetuses. These findings are in accordance with several examples in the animal and human literature that suggest that

NIH-PA Author Manuscript

NIH-PA Author Manuscript

NIH-PA Author Manuscript

many prenatal insults produce sexually dimorphic developmental consequences (65–69). Mechanisms that have been proposed to be involved in this phenomenon include sex-specific placental adaptation to stress exposure (70) and increased susceptibility of the female brain to its milieu given the more rapid neurodevelopmental trajectory in females compared with males (71, 72). Furthermore, these results suggest a greater susceptibility of the amygdala than of the hippocampus to elevated cortisol concentrations. The pattern of enlarged amygdala but unaltered hippocampus volume is consistent with studies of orphanage rearing and exposure to maternal postnatal depression (73–75). The similarity between the pattern of our findings and those from previous studies raises the question of whether the amygdala may be more susceptible than the hippocampus to stress and elevated glucocorticoid exposure. Although evidence in animals indicates that exposure to prenatal stress or excess glucocorticoids during gestation impairs the development of the hippocampus (76, 77), it is possible that the consequences of in utero stress exposure on the hippocampus may become apparent only at later stages (for example, during puberty or aging) or upon additional exposure to postnatal stress (65, 78, 79). Furthermore, it has been suggested that after exposure to insults, the hippocampus, but not the amygdala, has a high capability for regeneration (80).

The results also suggest a higher susceptibility of the right amygdala compared with the left amygdala to the effects of glucocorticoid exposure. This finding is consistent with previous evidence for an association between high anxiety and larger right amygdala volume (81) and right amygdala hyperactivity (82). It has been suggested that negative emotions are predominantly processed in the right but not the left amygdala (83), supporting a specific role of the right amygdala in affective disorders.

Slide 27: Study II—Maternal prepregnancy obesity and child ADHD symptoms

It is well established that a fetus developing in an inflammatory milieu is significantly more susceptible to subsequent development of various neurodevelopmental disorders (84). One particularly potent condition that produces an increased inflammatory milieu during gestation is maternal obesity (85). Consistent with this line of reasoning, maternal obesity before and during pregnancy has been associated with deficits in neurodevelopmental outcomes during childhood and adulthood, including ADHD (86).

We addressed which neurocognitive alterations underlie the association between maternal obesity and increased risk for child ADHD.

Slide 28: Study II overview

We assessed the association between maternal prepregnancy body mass index (BMI) and child ADHD risk and executive function as measured at 7 years of age. In these analyses, in addition to controlling for the covariates listed previously (slide 20), we excluded children whose mother or father had an ADHD diagnosis to limit the likelihood that any associations between maternal obesity and higher ADHD symptoms in the children reflected hereditary transmission of ADHD risk, which is plausible given the high comorbidity of obesity and ADHD. Furthermore, we controlled for child BMI in all analyses.

Slide 29: Results III

Maternal prepregnancy BMI, but not weight gain during pregnancy, was associated with subsequent child ADHD symptoms, as assessed with the CBCL (54) in the child at ~7 years age ($F_{1,158} = 4.80$, $P = 0.03$). There was a 2.8-fold increase in the prevalence of ADHD among children of obese mothers compared with those of nonobese mothers (48). *$P < 0.05$, **$P < 0.01$; error bars denote SEM.

NIH-PA Author Manuscript

NIH-PA Author Manuscript

NIH-PA Author Manuscript

Slide 30: Results IV

Maternal prepregnancy BMI, but not weight gain during pregnancy, was also associated with child performance on an objective continuous performance task (go/no-go task) that required the execution of an anticipated motor response or its active inhibition at 7 years age ($F_{1,157} = 8.38$, $P < 0.01$). Child executive function was assessed using the go/no-go task, which is widely used for assessment of neurocognitive impairment in ADHD patients (87, 88). Participants were primed to press a button as quickly as possible in response to the presentation of every letter, except for the letter "X." Overall efficiency of performance was assessed by a measure combining speed and accuracy by dividing the mean reaction time by the number of correct responses (89). A higher score indicates poorer performance, which is why this measure is referred to as "inverse efficiency" (90). The figure shows the ratio of reaction time to the total number of correct trials, with a higher score indicating poorer executive function. Omission errors represent instances when a child did not press the button when (s)he should have pressed it, and commission errors are instances when a child pressed the button when (s)he should not have pressed it. Additional analyses of reaction time and type of errors in children of obese mothers showed that maternal prepregnancy obesity was associated with inattentive or less efficient processing, as indicated by a high number of omission errors (49). $*P < 0.05$, $**P < 0.01$; error bars denote SEM.

Slide 31: Impaired child attention mediates the association between prepregnancy obesity and child ADHD symptoms

Impaired child executive function mediated the association between maternal prepregnancy obesity and child ADHD symptoms. This suggests that maternal obesity is associated with an altered trajectory of brain development, which could be mediated by a higher inflammatory milieu in obese mothers. $*P < 0.05$, $**P < 0.01$, $***P < 0.001$. β, standardized beta coefficient from regression analyses.

Slide 32: Conclusions

The findings from these studies support the notion that preconceptional and prenatal conditions may affect child brain development, with specific empirical evidence for outcomes related to cognitive and affective function and the size of limbic structures. These neurodevelopmental alterations may, in turn, have implications for subsequent risk of neuropsychiatric disorders. Evidence was provided for the existence of critical sensitive developmental periods, with most observed brain alterations being associated with variation in environmental conditions either before conception or during early gestation. The observed effects were independent of birth outcomes (e.g., birth weight, length of gestation). It is likely that other characteristics, such as the sex of the child and genotypic variation, may interact with the prenatal environment to influence vulnerability for specific outcomes.

Slide 33: Ongoing studies and future directions

I will next give an overview of the ongoing studies at the University of California, Irvine (UC Irvine) Development, Health and Disease Research Program.

Slide 34: Ongoing studies at the UC Irvine Development, Health and Disease Research Program

We are currently conducting a prospective, longitudinal follow-up study in a population-based cohort of children born to mothers who have been extensively characterized during pregnancy with measures of the maternal-placental-fetal endocrine and inflammatory milieu; clinical measures of obstetric complications; laboratory results of clinical and diagnostic tests; measures of maternal sociodemographic, behavioral, and psychosocial characteristics; measures of the birth phenotype; and banked samples of maternal biologic tissue and

NIH-PA Author Manuscript

NIH-PA Author Manuscript

NIH-PA Author Manuscript

extracted maternal and child DNA samples. A sample of 120 to 140 children from this cohort will be recruited at birth and followed until 12 months of age. We are conducting two major study assessments at 2 to 4 (time point 1, T1) weeks and at 12 months (time point two, T2) of age, during which we will measure brain morphology, white matter integrity, and functional connectivity. Brain morphology (size of the hippocampus, amygdala, and prefrontal cortex) will be determined from serial structural MRI scans. White matter integrity (indicators of myelination and how densely fibers are bundled in specific tracks) will be derived from serial diffusion tensor imaging (DTI) scans, and functional connectivity of fronto-limbic brain circuits will be derived from resting-state functional MRI (fMRI) scans. Infants' mental and motor development will also be assessed at T1 and T2 with the Test of Infant Motor Performance (TIMP) and Bayley Scales of Infant Development. Furthermore, we are using serial measures of parental stress, maternal sensitivity, maternal-child attachment, home environment, and child nutrition to assess the quality of the postnatal environment, which will allow us to test interactive pre- and postnatal influences on brain development. By providing neuroimaging data in human newborns and young infants and linking these outcomes to well-characterized measures of the intrauterine and early postnatal environment, we suggest that our study will set the stage for translational research with implications for early identification of risk and vulnerable populations and will thereby inform the subsequent development of primary and secondary intervention strategies.

Slide 35: Future directions

In the future, we would like to perform longer-term follow-up of infant and child brain development in those participants involved in the ongoing study that we just described. We would also like to address gene-environment interactions, including genes associated with risk for developmental disorders and psychopathology, such as those encoding serotonin transporters, the dopamine D4 receptor, and common variants of BDNF, such as $BDNF^{V66M}$. We want to perform additional assays on the biological specimens collected during pregnancy, such as quantifying the abundance of iron, nutrition biomarkers, omega-3 fatty acids, oxidative stress, insulin, and glucose. Finally, we aim to characterize the effects of exposure to biological stresses, such as high concentrations of glucocorticoids and pro-inflammatory cytokines, on neural stem cell differentiation in tissue culture.

Slide 36: Collaborators and acknowledgements

We particularly acknowledge the contributions of J. M. Swanson and S. G. Potkin for the development of many of the concepts presented here. The two empirical studies presented here were from a research project led by C. A. Sandman in collaboration with E. P. Davis and supported by NIH grants HD-51852 and HD-28413, respectively. The ongoing neuroimaging work is being performed in collaboration with J. H. Gilmore and M. Styner at the Univ. of North Carolina and D. Fair of the Oregon Health and Science Univ. under NIH grants MH-091351, HD-06028, and HD-065825, respectively.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

References

1. Geuze E, Vermetten E, Bremner JD. MR-based in vivo hippocampal volumetrics: 2. Findings in neuropsychiatric disorders. Mol. Psychiatry. 2005; 10:160–184. [PubMed: 15356639]
2. Bellani M, Baiano M, Brambilla P. Brain anatomy of major depression II. Focus on amygdala. Epidemiol Psychiatr Sci. 2011; 20:33–36. [PubMed: 21657113]

NIH-PA Author Manuscript

NIH-PA Author Manuscript

NIH-PA Author Manuscript

3. Gilbertson MW, Shenton ME, Ciszewski A, Kasai K, Lasko NB, Orr SP, Pitman RK. Smaller hippocampal volume predicts pathologic vulnerability to psychological trauma. Nat. Neurosci. 2002; 5:1242–1247. [PubMed: 12379862]
4. Hyman SE. A glimmer of light for neuropsychiatric disorders. Nature. 2008; 455:890–893. [PubMed: 18923510]
5. Andersen SL. Trajectories of brain development: Point of vulnerability or window of opportunity? Neurosci. Biobehav. Rev. 2003; 27:3–18. [PubMed: 12732219]
6. Gluckman PD, Hanson MA. Living with the past: Evolution, development, and patterns of disease. Science. 2004; 305:1733–1736. [PubMed: 15375258]
7. Swanson JD, Wadhwa PM. Developmental origins of child mental health disorders. J. Child Psychol. Psychiatry. 2008; 49:1009–1019. [PubMed: 19017021]
8. Kang HJ, Kawasawa YI, Cheng F, Zhu Y, Xu X, Li M, Sousa AM, Pletikos M, Meyer KA, Sedmak G, Guennel T, Shin Y, Johnson MB, Krsnik Z, Mayer S, Fertuzinhos S, Umlauf S, Lisgo SN, Vortmeyer A, Weinberger DR, Mane S, Hyde TM, Huttner A, Reimers M, Kleinman JE, Sestan N. Spatio-temporal transcriptome of the human brain. Nature. 2011; 478:483–489. [PubMed: 22031440]
9. Wadhwa PD, Entringer S, Buss C, Lu MC. The contribution of maternal stress to preterm birth: Issues and considerations. Clin. Perinatol. 2011; 38:351–384. [PubMed: 21890014]
10. Entringer S, Buss C, Swanson JM, Cooper DM, Wing DA, Waffarn F, Wadhwa PD. Fetal programming of body composition, obesity, and metabolic function: The role of intrauterine stress and stress biology. J. Nutr. Metab. 2012; 2012:632548. [PubMed: 22655178]
11. Uno H, Eisele S, Sakai A, Shelton S, Baker E, DeJesus O, Holden J. Neurotoxicity of glucocorticoids in the primate brain. Horm. Behav. 1994; 28:336–348. [PubMed: 7729802]
12. Bose R, Moors M, Tofighi R, Cascante A, Hermanson O, Ceccatelli S. Glucocorticoids induce long-lasting effects in neural stem cells resulting in senescence-related alterations. Cell Death Dis. 2010; 1:e92. [PubMed: 21368868]
13. Moors M, Bose R, Johansson-Haque K, Edoff K, Okret S, Ceccatelli S. Dickkopf 1 mediates glucocorticoid-induced changes in human neural progenitor cell proliferation and differentiation. Toxicol. Sci. 2012; 125:488–495. [PubMed: 22048647]
14. Crampton SJ, Collins LM, Toulouse A, Nolan YM, O'Keeffe GW. Exposure of foetal neural progenitor cells to IL-1β impairs their proliferation and alters their differentiation - A role for maternal inflammation? J. Neurochem. 2012; 120:964–973. [PubMed: 22192001]
15. Guo R, Hou W, Dong Y, Yu Z, Stites J, Weiner CP. Brain injury caused by chronic fetal hypoxemia is mediated by inflammatory cascade activation. Reprod. Sci. 2010; 17:540–548. [PubMed: 20360591]
16. Wei H, Zou H, Sheikh AM, Malik M, Dobkin C, Brown WT, Li X. IL-6 is increased in the cerebellum of autistic brain and alters neural cell adhesion, migration and synaptic formation. Neuroinflammation. 2011; 8:52.
17. Huang WL, Harper CG, Evans SF, Newnham JP, Dunlop SA. Repeated prenatal corticosteroid administration delays myelination of the corpus callosum in fetal sheep. Int. J. Dev. Neurosci. 2001; 19:415–425. [PubMed: 11378301]
18. Elovitz MA, Mrinalini C, Sammel MD. Elucidating the early signal transduction pathways leading to fetal brain injury in preterm birth. Pediatr. Res. 2006; 59:50–55. [PubMed: 16327009]
19. O'Shea TM. Cerebral palsy in very preterm infants: New epidemiological insights. Ment. Retard. Dev. Disabil. Res. Rev. 2002; 8:135–145. [PubMed: 12216057]
20. Rezaie P, Dean A. Periventricular leukomalacia, inflammation and white matter lesions within the developing nervous system. Neuropathology. 2002; 22:106–132. [PubMed: 12416551]
21. Graciarena M, Depino AM, Pitossi FJ. Prenatal inflammation impairs adult neurogenesis and memory related behavior through persistent hippocampal TGFβ downregulation. Brain Behav. Immun. 2010; 24:1301–1309. [PubMed: 20600816]
22. Golan HM, Lev V, Hallak M, Sorokin Y, Huleihel M. Specific neurodevelopmental damage in mice offspring following maternal inflammation during pregnancy. Neuropharmacology. 2005; 48:903–917. [PubMed: 15829260]

NIH-PA Author Manuscript

NIH-PA Author Manuscript

NIH-PA Author Manuscript

23. Vuillermot S, Weber L, Feldon J, Meyer U. A longitudinal examination of the neurodevelopmental impact of prenatal immune activation in mice reveals primary defects in dopaminergic development relevant to schizophrenia. J. Neurosci. 2010; 30:1270–1287. [PubMed: 20107055]
24. Delany AM, Durant D, Canalis E. Glucocorticoid suppression of IGF I transcription in osteoblasts. Mol. Endocrinol. 2001; 15:1781–1789. [PubMed: 11579210]
25. Brabant A, Brabant G, Schuermeyer T, Ranft U, Schmidt FW, Hesch RD, von zur Mühlen A. The role of glucocorticoids in the regulation of thyrotropin. Acta Endocrinol. (Copenh.). 1989; 121:95–100. [PubMed: 2500822]
26. Yamazaki K, Yamada E, Kanaji Y, Shizume K, Wang DS, Maruo N, Obara T, Sato K. Interleukin-6 (IL-6) inhibits thyroid function in the presence of soluble IL-6 receptor in cultured human thyroid follicles. Endocrinology. 1996; 137:4857–4863. [PubMed: 8895357]
27. Ozawa M, Sato K, Han DC, Kawakami M, Tsushima T, Shizume K. Effects of tumor necrosis factor-α/cachectin on thyroid hormone metabolism in mice. Endocrinology. 1988; 123:1461–1467. [PubMed: 3402392]
28. Fowden AL, Forhead AJ. Endocrine regulation of feto-placental growth. Horm. Res. 2009; 72:257–265. [PubMed: 19844111]
29. Entringer S, Buss C, Wadhwa PD. Prenatal stress and developmental programming of human health and disease risk: Concepts and integration of empirical findings. Curr. Opin. Endocrinol. Diabetes Obes. 2010; 17:507–516. [PubMed: 20962631]
30. Shimizu H, Arima H, Ozawa Y, Watanabe M, Banno R, Sugimura Y, Ozaki N, Nagasaki H, Oiso Y. Glucocorticoids increase NPY gene expression in the arcuate nucleus by inhibiting mTOR signaling in rat hypothalamic organotypic cultures. Peptides. 2010; 31:145–149. [PubMed: 19818818]
31. Heine VM, Rowitch DH. Hedgehog signaling has a protective effect in glucocorticoid-induced mouse neonatal brain injury through an 11betaHSD2-dependent mechanism. J. Clin. Invest. 2009; 119:267–277. [PubMed: 19164857]
32. Lussier AL, Caruncho HJ, Kalynchuk LE. Repeated exposure to corticosterone, but not restraint, decreases the number of reelin-positive cells in the adult rat hippocampus. Neurosci. Lett. 2009; 460:170–174. [PubMed: 19477232]
33. Skaper SD. The neurotrophin family of neurotrophic factors: An overview. Methods Mol. Biol. 2012; 846:1–12. [PubMed: 22367796]
34. Kumamaru E, Numakawa T, Adachi N, Yagasaki Y, Izumi A, Niyaz M, Kudo M, Kunugi H. Glucocorticoid prevents brain-derived neurotrophic factor-mediated maturation of synaptic function in developing hippocampal neurons through reduction in the activity of mitogen-activated protein kinase. Mol. Endocrinol. 2008; 22:546–558. [PubMed: 18096693]
35. Janusonis S, Gluncic V, Rakic P. Early serotonergic projections to Cajal-Retzius cells: Relevance for cortical development. J. Neurosci. 2004; 24:1652–1659. [PubMed: 14973240]
36. Price CJ, Goldberg JI. Serotonin activation of a cyclic AMP-dependent sodium current in an identified neuron from *Helisoma trivolvis*. J. Neurosci. 1993; 13:4979–4987. [PubMed: 7693898]
37. Udo H, Jin I, Kim JH, Li HL, Youn T, Hawkins RD, Kandel ER, Bailey CH. Serotonin-induced regulation of the actin network for learning-related synaptic growth requires Cdc42, N-WASP, and PAK in Aplysia. sensory neurons. Neuron. 2005; 45:887–901. [PubMed: 15797550]
38. Papaioannou A, Dafni U, Alikaridis F, Bolaris S, Stylianopoulou F. Effects of neonatal handling on basal and stress-induced monoamine levels in the male and female rat brain. Neuroscience. 2002; 114:195–206. [PubMed: 12207965]
39. Winter C, Djodari-Irani A, Sohr R, Morgenstern R, Feldon J, Juckel G, Meyer U. Prenatal immune activation leads to multiple changes in basal neurotransmitter levels in the adult brain: Implications for brain disorders of neurodevelopmental origin such as schizophrenia. Int. J. Neuropsychopharmacol. 2009; 12:513–524. [PubMed: 18752727]
40. Aberg ND, Blomstrand F, Aberg MA, Björklund U, Carlsson B, Carlsson-Skwirut C, Bang P, Rönnbäck L, Eriksson PS. Insulin-like growth factor-I increases astrocyte intercellular gap junctional communication and connexin43 expression in vitro. J. Neurosci. Res. 2003; 74:12–22. [PubMed: 13130502]

NIH-PA Author Manuscript

NIH-PA Author Manuscript

NIH-PA Author Manuscript

41. Feldman EL, Sullivan KA, Kim B, Russell JW. Insulin-like growth factors regulate neuronal differentiation and survival. Neurobiol. Dis. 1997; 4:201–214. [PubMed: 9361296]
42. Pathak A, Sinha RA, Mohan V, Mitra K, Godbole MM. Maternal thyroid hormone before the onset of fetal thyroid function regulates reelin and downstream signaling cascade affecting neocortical neuronal migration. Cereb. Cortex. 2011; 21:11–21. [PubMed: 20368265]
43. Chen C, Zhou Z, Zhong M, Zhang Y, Li M, Zhang L, Qu M, Yang J, Wang Y, Yu Z. Thyroid hormone promotes neuronal differentiation of embryonic neural stem cells by inhibiting STAT3 signaling through TRα1. Stem Cells Dev. 2012; 21:2667–2681. [PubMed: 22468949]
44. Desouza LA, Sathanoori M, Kapoor R, Rajadhyaksha N, Gonzalez LE, Kottmann AH, Tole S, Vaidya VA. Thyroid hormone regulates the expression of the sonic hedgehog signaling pathway in the embryonic and adult Mammalian brain. Endocrinology. 2011; 152:1989–2000. [PubMed: 21363934]
45. Clancy B, Darlington RB, Finlay BL. Translating developmental time across mammalian species. Neuroscience. 2001; 105:7–17. [PubMed: 11483296]
46. Anderson BJ. Plasticity of gray matter volume: The cellular and synaptic plasticity that underlies volumetric change. Dev. Psychobiol. 2011; 53:456–465. [PubMed: 21678393]
47. Kraft E. Cognitive function, physical activity, and aging: Possible biological links and implications for multimodal interventions. Neuropsychol. Dev. Cogn. B. Aging Neuropsychol. Cogn. 2012; 19:248–263. [PubMed: 22313174]
48. Buss C, Davis EP, Shahbaba B, Pruessner JC, Head K, Sandman CA. Maternal cortisol over the course of pregnancy and subsequent child amygdala and hippocampus volumes and affective problems. Proc. Natl. Acad. Sci. U.S.A. 2012; 109:E1312–E1319. [PubMed: 22529357]
49. Buss C, Entringer S, Davis EP, Hobel CJ, Swanson JM, Wadhwa PD, Sandman CA. Impaired executive function mediates the association between maternal pre-pregnancy body mass index and child ADHD symptoms. PLoS ONE. 2012; 7:e37758. [PubMed: 22719848]
50. Chrousos GP, Kino T. Glucocorticoid signaling in the cell. Expanding clinical implications to complex human behavioral and somatic disorders. Ann. N.Y. Acad. Sci. 2009; 1179:153–166. [PubMed: 19906238]
51. Chrousos GP, Gold PW. The concepts of stress and stress system disorders. Overview of physical and behavioral homeostasis. JAMA. 1992; 267:1244–1252. [PubMed: 1538563]
52. Harris A, Seckl J. Glucocorticoids, prenatal stress and the programming of disease. Horm. Behav. 2011; 59:279–289. [PubMed: 20591431]
53. Davis EP, Sandman CA. The timing of prenatal exposure to maternal cortisol and psychosocial stress is associated with human infant cognitive development. Child Dev. 2010; 81:131–148. [PubMed: 20331658]
54. Achenbach, TM.; Rescorla, LA. Manual for the ASEBA School-Age Forms and Profiles. Burlington, VT: Univ. of Vermont Research Centre for Children, Youth, and Families; 2001.
55. Beitins IZ, Bayard F, Ances IG, Kowarski A, Migeon CJ. The metabolic clearance rate, blood production, interconversion and transplacental passage of cortisol and cortisone in pregnancy near term. Pediatr. Res. 1973; 7:509–519. [PubMed: 4704743]
56. Brown RW, Diaz R, Robson AC, Kotelevtsev YV, Mullins JJ, Kaufman MH, Seckl JR. The ontogeny of 11 β-hydroxysteroid dehydrogenase type 2 and mineralocorticoid receptor gene expression reveal intricate control of glucocorticoid action in development. Endocrinology. 1996; 137:794–797. [PubMed: 8593833]
57. Benediktsson R, Calder AA, Edwards CR, Seckl JR. Placental 11 β-hydroxysteroid dehydrogenase: A key regulator of fetal glucocorticoid exposure. Clin. Endocrinol. (Oxf.). 1997; 46:161–166. [PubMed: 9135697]
58. O'Donnell KJ, Bugge Jensen A, Freeman L, Khalife N, O'Connor TG, Glover V. Maternal prenatal anxiety and downregulation of placental 11β-HSD2. Psychoneuroendocrinology. 2012; 37:818–826. [PubMed: 22001010]
59. Johnstone JF, Bocking AD, Unlugedik E, Challis JR. The effects of chorioamnionitis and betamethasone on 11β hydroxysteroid dehydrogenase types 1 and 2 and the glucocorticoid receptor in preterm human placenta. J. Soc. Gynecol. Investig. 2005; 12:238–245.

NIH-PA Author Manuscript

NIH-PA Author Manuscript

NIH-PA Author Manuscript

60. Kossintseva I, Wong S, Johnstone E, Guilbert L, Olson DM, Mitchell BF. Proinflammatory cytokines inhibit human placental 11β-hydroxysteroid dehydrogenase type 2 activity through Ca^{2+} and cAMP pathways. Am. J. Physiol. Endocrinol. Metab. 2006; 290:E282–E288. [PubMed: 16174654]
61. Liang G, Chen M, Pan XL, Zheng J, Wang H. Ethanol-induced inhibition of fetal hypothalamic-pituitary-adrenal axis due to prenatal overexposure to maternal glucocorticoid in mice. Exp. Toxicol. Pathol. 2011; 63:607–611. [PubMed: 20627497]
62. Cheng YH, Nicholson RC, King B, Chan EC, Fitter JT, Smith R. Glucocorticoid stimulation of corticotropin-releasing hormone gene expression requires a cyclic adenosine 3′,5′-monophosphate regulatory element in human primary placental cytotrophoblast cells. J. Clin. Endocrinol. Metab. 2000; 85:1937–1945. [PubMed: 10843178]
63. Rehman KS, Sirianni R, Parker CR Jr, Rainey WE, Carr BR. The regulation of adrenocorticotrophic hormone receptor by corticotropin-releasing hormone in human fetal adrenal definitive/transitional zone cells. Reprod. Sci. 2007; 14:578–587. [PubMed: 17959886]
64. Sandman CA, Glynn L, Schetter CD, Wadhwa P, Garite T, Chicz-DeMet A, Hobel C. Elevated maternal cortisol early in pregnancy predicts third trimester levels of placental corticotropin releasing hormone (CRH): Priming the placental clock. Peptides. 2006; 27:1457–1463. [PubMed: 16309788]
65. Buss C, Lord C, Wadiwalla M, Hellhammer DH, Lupien SJ, Meaney MJ, Pruessner JC. Maternal care modulates the relationship between prenatal risk and hippocampal volume in women but not in men. J. Neurosci. 2007; 27:2592–2595. [PubMed: 17344396]
66. Buss C, Davis EP, Hobel CJ, Sandman CA. Maternal pregnancy-specific anxiety is associated with child executive function at 6–9 years age. Stress. 2011; 14:665–676. [PubMed: 21995526]
67. Behan AT, van den Hove DL, Mueller L, Jetten MJ, Steinbusch HW, Cotter DR, Prickaerts J. Evidence of female-specific glial deficits in the hippocampus in a mouse model of prenatal stress. Eur. Neuropsychopharmacol. 2011; 21:71–79. [PubMed: 20702067]
68. Zohar I, Weinstock M. Differential effect of prenatal stress on the expression of corticotrophin-releasing hormone and its receptors in the hypothalamus and amygdala in male and female rats. J. Neuroendocrinol. 2011; 23:320–328. [PubMed: 21306450]
69. Bale TL. Sex differences in prenatal epigenetic programming of stress pathways. Stress. 2011; 14:348–356. [PubMed: 21663536]
70. Clifton VL. Review: Sex and the human placenta: mediating differential strategies of fetal growth and survival. Placenta. 2010; 31(suppl.):S33–S39. [PubMed: 20004469]
71. Buss C, Davis EP, Class QA, Gierczak M, Pattillo C, Glynn LM, Sandman CA. Maturation of the human fetal startle response: Evidence for sex-specific maturation of the human fetus. Early Hum. Dev. 2009; 85:633–638. [PubMed: 19726143]
72. Nathanielsz PW, Berghorn KA, Derks JB, Giussani DA, Docherty C, Unno N, Davenport A, Kutzlers M, Koenen S, Visser GH, Nijland MJ. Life before birth: Effects of cortisol on future cardiovascular and metabolic function. Acta Paediatr. 2003; 92:766–772. [PubMed: 12894758]
73. Lupien SJ, Parent S, Evans AC, Tremblay RE, Zelazo PD, Corbo V, Pruessner JC, Sèguin JR. Larger amygdala but no change in hippocampal volume in 10-year-old children exposed to maternal depressive symptomatology since birth. Proc. Natl. Acad. Sci. U.S.A. 2011; 108:14324–14329. [PubMed: 21844357]
74. Tottenham N, Hare TA, Quinn BT, Mc-Carry TW, Nurse M, Gilhooly T, Millner A, Galvan A, Davidson MC, Eigsti IM, Thomas KM, Freed PJ, Booma ES, Gunnar MR, Altemus M, Aronson J, Casey BJ. Prolonged institutional rearing is associated with atypically large amygdala volume and difficulties in emotion regulation. Dev. Sci. 2010; 13:46–61. [PubMed: 20121862]
75. Mehta MA, Golembo NI, Nosarti C, Colvert E, Mota A, Williams SC, Rutter M, Sonuga-Barke EJ. Amygdala, hippocampal and corpus callosum size following severe early institutional deprivation: The English and Romanian Adoptees study pilot. J. Child Psychol. Psychiatry. 2009; 50:943–951. [PubMed: 19457047]
76. Jia N, Yang K, Sun Q, Cai Q, Li H, Cheng D, Fan X, Zhu Z. Prenatal stress causes dendritic atrophy of pyramidal neurons in hippocampal CA3 region by glutamate in offspring rats. Dev. Neurobiol. 2010; 70:114–125. [PubMed: 19950194]

NIH-PA Author Manuscript

NIH-PA Author Manuscript

NIH-PA Author Manuscript

77. Coe CL, Kramer M, Czèh B, Gould E, Reeves AJ, Kirschbaum C, Fuchs E. Prenatal stress diminishes neurogenesis in the dentate gyrus of juvenile rhesus monkeys. Biol. Psychiatry. 2003; 54:1025–1034. [PubMed: 14625144]

78. Meaney MJ, Aitken DH, Bhatnagar S, Sapolsky RM. Postnatal handling attenuates certain neuroendocrine, anatomical, and cognitive dysfunctions associated with aging in female rats. Neurobiol. Aging. 1991; 12:31–38. [PubMed: 2002881]

79. Koehl M, Lemaire V, Le Moal M, Abrous DN. Age-dependent effect of prenatal stress on hippocampal cell proliferation in female rats. Eur. J. Neurosci. 2009; 29:635–640. [PubMed: 19238600]

80. Vyas A, Pillai AG, Chattarji S. Recovery after chronic stress fails to reverse amygdaloid neuronal hypertrophy and enhanced anxiety-like behavior. Neuroscience. 2004; 128:667–673. [PubMed: 15464275]

81. De Bellis MD, Casey BJ, Dahl RE, Birmaher B, Williamson DE, Thomas KM, Axelson DA, Frustaci K, Boring AM, Hall J, Ryan ND. A pilot study of amygdala volumes in pediatric generalized anxiety disorder. Biol. Psychiatry. 2000; 48:51–57. [PubMed: 10913507]

82. Juranek J, Filipek PA, Berenji GR, Modahl C, Osann K, Spence MA. Association between amygdala volume and anxiety level: Magnetic resonance imaging (MRI) study in autistic children. J. Child Neurol. 2006; 21:1051–1058. [PubMed: 17156697]

83. Demaree HA, Everhart DE, Youngstrom EA, Harrison DW. Brain lateralization of emotional processing: Historical roots and a future incorporating “dominance”. Behav. Cogn. Neurosci. Rev. 2005; 4:3–20. [PubMed: 15886400]

84. Bilbo SD, Schwarz JM. Early-life programming of later-life brain and behavior: A critical role for the immune system. Front. Behav.. Neurosci. 2009; 3:14. [PubMed: 19738918]

85. Huda SS, Brodie LE, Sattar N. Obesity in pregnancy: Prevalence and metabolic consequences. Semin. Fetal Neonatal Med. 2010; 15:70–76. [PubMed: 19896913]

86. Van Lieshout RJ, Taylor VH, Boyle MH. Prepregnancy and pregnancy obesity and neurodevelopmental outcomes in offspring: A systematic review. Obes. Rev. 2011; 12:e548–e559. [PubMed: 21414129]

87. Epstein JN, Erkanli A, Conners CK, Klaric J, Costello JE, Angold A. Relations between Continuous Performance Test performance measures and ADHD behaviors. J. Abnorm. Child Psychol. 2003; 31:543–554. [PubMed: 14561061]

88. Willcutt EG, Doyle AE, Nigg JT, Faraone SV, Pennington BF. Validity of the executive function theory of attention-deficit/hyperactivity disorder: A meta-analytic review. Biol. Psychiatry. 2005; 57:1336–1346. [PubMed: 15950006]

89. Townsend, JT.; Ashby, FG. Stochastic Modelling of Elementary Psychological Processes. New York: Cambridge Univ. Press; 1983.

90. Mullane JC, Corkum PV, Klein RM, McLaughlin E. Interference control in children with and without ADHD: A systematic review of Flanker and Simon task performance. Child Neuropsychol. 2009; 15:321–342. [PubMed: 18850349]