Does prenatal stress alter the developing connectome?

Dustin Scheinost1, Rajita Sinha2,3,4, Sarah N. Cross5, Soo Hyun Kwon6, Gordon Sze1, R. Todd Constable7,8 and Laura R. Ment9,10

Human neurodevelopment requires the organization of neural elements into complex structural and functional networks called the connectome. Emerging data suggest that prenatal exposure to maternal stress plays a role in the wiring, or miswiring, of the developing connectome. Stress-related symptoms are common in women during pregnancy and are risk factors for neurobehavioral disorders ranging from autism spectrum disorder, attention deficit hyperactivity disorder, and addiction, to major depression and schizophrenia. This review focuses on structural and functional connectivity imaging to assess the impact of changes in women's stress-based physiology on the dynamic development of the human connectome in the fetal brain.

Human neurodevelopment requires the organization of neural elements into complex structural and functional networks called the connectome (1–3). While development of the connectome is contingent on many factors, emerging data suggest that prenatal exposure to maternal stress may also play a role (4–7). Stress is a signal in response to challenging and uncontrollable adverse events and perceived threat (8,9), and exposure to early life stress is a risk factor for neurobehavioral disorders ranging from autism spectrum disorder (ASD), attention deficit hyperactivity disorder and addiction, to depression and schizophrenia (10–21). Both high stress and stress-related conditions, including depression and anxiety, potently stimulate biological stress pathways (7), alter synaptogenesis (22,23), and change brain development (5,24–28). The prenatal period is critical for brain development, and prenatal stressors exhibit long-lasting influence on adult disorders, making stressor type and timing important factors to explore (27,29,30). Fetal sex and genetic variants may also mediate stress responsiveness (6,7,31–34).

Recent reports suggest that prenatal stress exposure (PNSE) is a global public health problem (13,29,35,36). PNSE has been reported in 10–35% of children worldwide (37). Nearly 8–23% of infants in the United States, or almost 800,000 neonates/year, experience prenatal exposure to depression (38,39), and reports from developing countries support similar numbers (40–42). Likewise, 1 in 7 to 1 in 13 pregnant women in the United States affirm symptoms of anxiety, while 5.6–14.8% in developing countries suffer a similar diagnosis (40–44). Since a nationally representative study found that more than half of the pregnant women (65.9%) experiencing depression in the United States went undiagnosed (45), these data may underestimate the problem.

PNSE is believed to both activate the hypothalamic-pituitary-adrenal (HPA) axis and result in epigenetic changes in the developing brain. This review will focus on converging preclinical and clinical imaging data to assess the impact of these changes in women's stress-based physiology on the functional development of the human fetal brain. Prior to reviewing published data, we review common causes of PNSE and methods for measuring the structural and functional connectome. We also provide preliminary human data demonstrating increasing connectivity in limbic system structures across the third trimester of gestation.

STRESS MODELS IN CLINICAL AND TRANSLATIONAL STUDIES

While the relationship between maternal psychosocial stress and adverse pregnancy outcomes has been shown in many studies, it is important to define the nature of the stressor and the subject population (46). Stressors range from depression and anxiety to natural disasters, bereavement and steroid administration. As stressors vary, so may the outcomes. For a listing of outcomes, putative prenatal stressors and representative publications, please see Table 1.

Depression and Anxiety

Although some older studies relied on retrospective recall measures and few evaluated the effects of increasing duration and strength of psychosocial stressors, more recent investigations have employed depression and anxiety as markers of maternal stress. Estimates suggest that 8–23% of women have symptoms of depression during their pregnancy (47). Likewise, 7.7–14% report anxiety, and there are numerous reports of coexisting depression and anxiety in the same pregnant woman at any given time. While depression and anxiety are common proxies...
Preconception Stress

In contrast, the influence of preconception adversity and the impact of high cumulative stress on maternal perception of prenatal stress on the developing connectome are just beginning to be explored (53–55). Consistent with preclinical studies showing effects of repeated stress on neural atrophy and neurobehavioral effects (56), human studies link altered structure and function of limbic, subcortical, and frontal regions to higher levels of cumulative stress (28,57,58). These data suggest that preconception adversity may shape perception and control of prenatal stress levels and should be considered in investigations of PNSE on neurobehavioral and MRI outcomes.

Prenatal Maternal Stress

PNSE has been widely associated with preterm birth, intrauterine growth restriction, and reduced fetal head growth (50,51,59–61). In addition, several studies have reported that increased acute maternal stress is associated with changes in fetal heart rate, activity level, sleep patterns, and higher pulsatility indices in the middle cerebral artery (21,60). PNSE can also be directly measured using prospective data collections in samples of pregnant women with questionnaires, clinical interviews, and biological samples such as cortisol from maternal saliva, blood, or amniotic fluid.

METHODS TO ASSESS CONNECTIVITY USING MRI

Advances in neuroimaging provide important information about microstructural and functional connectivity (62), and offer opportunities to understand the impact of PNSE on the developing connectome (1–3). In the following section, we define measures commonly used in connectomics with examples shown in Figure 1.

Functional connectivity provides information about neural regions that are physiologically functionally coupled, independent of structural connectivity (63). Based on the blood oxygen level dependent signal and derived from time series observations, it assesses “temporal correlations between spatially remote neurophysiological events.” (63) High correlation between time courses of two regions or voxels implies high functional connectivity. For the references included in this review, functional MRI (fMRI) data are largely collected in the resting state, or resting state-fMRI (rs-fMRI).

Methods to assess rs-fMRI data (64,65) include seed, independent components analysis, and voxel-wise connectivity. Seed-based connectivity is most frequently used in human studies and involves (i) selecting a predefined region of interest (ROI), (ii) extracting the average time course from this ROI, and (iii) correlating this average time course with the time courses of every other voxel in the gray matter. Independent components analysis is mathematical modeling technique that parcellates the brain into independent spatial components or networks. These networks can be compared across subject groups or used for later analysis. Voxel-wise connectivity methods are generalizations of seed-based connectivity where many seed connectivity analyses are performed treating each voxel in the gray matter as a unique ROI. As these methods

for stress, stress in pregnant women does not always coincide with elevated depression or anxiety scales. As such, cases of PNSE may be missed in such analysis. Finally, depression and anxiety may have independent or additive effects in regards to PNSE, making it difficult to fully disentangle these effects with this model. For a more complete review of this topic, please see Suri et al. (48).

Natural Disasters

Another approach to test the hypothesis that PNSE results in neurobehavioral disorders is the use of natural disasters as “experiments of nature.” Unlike depression and anxiety, natural disasters are independent of the subject’s genetic background, personality or other confounding characteristics. Disasters strike in a random manner, similar to a randomized controlled experiment, and thus can provide data on prenatal stressors to which a given cohort of pregnant women were exposed (13). Using this strategy, the impact of disasters ranging from hurricanes to terrorist attacks on neurobehavioral outcomes of the offspring have been assessed (13,49–52).

Table 1. Disorders and putative prenatal stressors

| Disorder                          | Prenatal stress and representative references |
|----------------------------------|-----------------------------------------------|
| Autism spectrum disorder         | Anxiety (13,103), Conjugal conflict (104) | Natural disasters (13,52) |
| Attention deficit hyperactivity disorder | Anxiety (61,103,107,108) | Maternal bereavement (15,55) |
| Bipolar affective disorder       | Stress (109)                                  |
| Cognition                        | Anxiety (107,110)                              | Depression (48) |
| Depression                       | Depression (16,48,113)                         | PTSD (113) |
| Internalizing problems           | Depression (114)                              |
| Neonatal behavioral changes      | Anxiety (115,116)                             | Depression (48,115,117) |
| Pervasive developmental disorder | Depression (53)                               |
| Psychosis                        | Cumulative life experiences (120,121)         | Depression (121) |
| Schizophrenia                    | PTSD (122,123)                                |

PTSD, post-traumatic stress disorder.

Table 1. Disorders and putative prenatal stressors

| Disorder                          | Prenatal stress and representative references |
|----------------------------------|-----------------------------------------------|
| Autism spectrum disorder         | Anxiety (13,103), Conjugal conflict (104) | Natural disasters (13,52) |
| Attention deficit hyperactivity disorder | Anxiety (61,103,107,108) | Maternal bereavement (15,55) |
| Bipolar affective disorder       | Stress (109)                                  |
| Cognition                        | Anxiety (107,110)                              | Depression (48) |
| Depression                       | Depression (16,48,113)                         | PTSD (113) |
| Internalizing problems           | Depression (114)                              |
| Neonatal behavioral changes      | Anxiety (115,116)                             | Depression (48,115,117) |
| Pervasive developmental disorder | Depression (53)                               |
| Psychosis                        | Cumulative life experiences (120,121)         | Depression (121) |
| Schizophrenia                    | PTSD (122,123)                                |

PTSD, post-traumatic stress disorder.
The three main approaches to analyzing dMRI data include region ROI quantification, tract-based analysis and tractography, and voxel-based morphometry (VBM). ROI quantification is frequently used in human studies investigating the impact of PNSE on the developing connectome. In this method, one or more ROIs are selected a priori and the average FA across all voxels in the ROI calculated. Typically, ROIs are major white matter tracts. Tractography is modeling technique used to identify these tracts. Once identified, they can be analyzed using graph theory or ROI analyses. In VBM analysis, FA data from all subjects are transformed into a common space and compared across each voxel of the white matter.

Finally, although not direct measures of the connectome, we include studies assessing brain morphometry, including cortical volumes and thickness. Morphological features of different brain regions are not independent of those of other areas, and the brain shows a high level of coordination between different structures (67). This coordination of morphological features is often referred to as anatomical covariance (67–69) and resembles functional and structural connectivity.

PRECLINICAL DATA SUPPORT THE IMPACT OF PNSE ON DEVELOPING CONNECTOME

Across multiple species and numerous time points, converging data suggest that gestational stress influences brain development. Similar to the human subjects, the offspring of numerous species exposed to PNSE demonstrate increases in anxiety and depression, impaired spatial memory and alterations in cognition (70,71). Systematic experimental investigations using standardized animal models and outcome measures (6,72,73) address not only the impact of PNSE on maternal HPA axis (74–79), but also suggest that changes in corticogenesis contribute to the long-lasting effects on brain and behavior (Table 2) (74,80,81).

MRI STUDIES OF PNSE AND THE DEVELOPING BRAIN

While the neural correlates of acute and cumulative postnatal stress in human subjects are active fields of study, MRI research investigating PNSE in human subjects is just starting to be explored. As described below and shown in Table 3, many investigators have interrogated the impact of PNSE on the limbic system and connected regions in the developing brain.

Studies During Infancy

Recent studies suggest a significant relationship between antenatal maternal depression and/or anxiety and structure and
| Author/year | Model | Protocol—fetuses | Outcome                                                                 |
|-------------|-------|-----------------|--------------------------------------------------------------------------|
| Jutapakdeegul 2010 (124) | Pregnant rats Restraint stress Or Corticosterone 40mg/kg/d E14 – E21 | Quantitative immuno-histochemistry Levels of GAP-43 PND 7, 14 and 60 | GAP-43 increased in prefrontal cortex (PFC) at PND 7 and 14<br>GAP-43 decreased in PFC at PND 60<br>Results identical for prenatal stress and corticosterone injection studies<br>Corticosterone resulted in significant increase of GAP-43 and pGAP-43 in the hippocampus at PND 7 and PND 14 |
| Afadlal 2010 (125) | Pregnant rats Corticosterone 40 mg/kg/d E14 – E21 | Quantitative immuno-histochemistry Levels of GAP-43, pGAP-43 and synaptophysin in the hippocampus | Significant decrease in synaptophysin in hippocampus at same time points<br>Within 24h after treatment, betamethasone reduced number of mature oligodendrocytes and MBP immunoreactivity<br>Maternal and fetal treatment had similar outcomes<br>Loss of MBP immunoreactivity was not reversed 20 d after two treatment courses |
| Antonow-Schlorke 2009 (126) | Pregnant sheep Third trimester Betamethasone at 0.63, 0.75 and 0.87 gestation intramuscularly to mother or 48 h continuous infusion to fetus at 0.75 and 0.87 gestation | Immunohistochemistry – myelin basic protein (MBP) | Betamethasone resulted in a change in the formation of the myelin sheath in the commissural fibers of the corpus callosum but not in the association fibers of the subcortical white matter |
| Raschke 2008 (127) | Pregnant sheep Betamethasone administered at E 106/147 and E116/147 Lambs delivered preterm at 129/147 d gestation | Electron microscopy | Stress upregulated miR-219, a suppressor of neural stem cells<br>Stress also upregulated miR-98, an miRNA shown to decrease the cerebral inflammatory response and increase blood brain barrier tightness<br>Transcriptomic changes included genes related to development, axonal guidance and neuropathology<br>Delay in embryonic neurogenesis of GABAergic progenitors<br>PV-positive GABAergic neurons decreased in medial PFC, hippocampus (HPC) and somatosensory cortex of GAD67+/GFP but not wild-type offspring |
| Brain structure | Zucchi 2013 (128) | Prenatal stress | Offspring brain miRNA | Stress upregulated miR-219, a suppressor of neural stem cells<br>Stress also upregulated miR-98, an miRNA shown to decrease the cerebral inflammatory response and increase blood brain barrier tightness<br>Transcriptomic changes included genes related to development, axonal guidance and neuropathology<br>Delay in embryonic neurogenesis of GABAergic progenitors<br>PV-positive GABAergic neurons decreased in medial PFC, hippocampus (HPC) and somatosensory cortex of GAD67+/GFP but not wild-type offspring |
| Uchida 2014 (129) | GAD67-green fluorescent protein (GFP) knock-in pregnant mice Restraint and light stress from E 15.0 – E17.5 | Outcomes at PND 21 Immunohistochemistry Parvalbumin-(PV)positive interneurons | Delay in embryonic neurogenesis of GABAergic progenitors<br>PV-positive GABAergic neurons decreased in medial PFC, hippocampus (HPC) and somatosensory cortex of GAD67+/GFP but not wild-type offspring |
| Stevens 2013 (130) | Pregnant CAD67/GFP transgenic mice Restraint stress E12 onwards | Unbiased cell counting Immunohistochemistry | Migration of GABAergic progenitors to cortex delayed in PNSE<br>Significant changes in dlx2 and nkx2.1, transcription factors which regulate interneuron migration in PNSE forebrain<br>No change mash 1 (determinant of interneuron fate), bdnf (maturation factor for GABAergic cells) or fgf2 (growth/differentiation factor) |
| Lussier 2016 (80) | Pregnant mice Restraint stress E12-birth Male offspring only | Cell counting Immunohistochemistry Quantitative PCR | Parvalbumin neuron proportion in juvenile brain was altered by PNSE but parvalbumin gene expression showed no changes<br>PNS exhibit behavior changes which correlate with GABAergic populations in medial PFC and HPC<br>Total GABAergic cell number showed altered trajectories in medial PFC and HPC in PNSE mice |
### Table 2. Continued

| Author/year      | Model                  | Protocol—fetuses                                                                 | Outcome                                                                                   |
|------------------|------------------------|----------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------|
| Ehrlich 2015 (131) | Pregnant rats          | Amygdala GABA interneuron expression Cl- transporters KCC2 and NKCC1            | PNS E decreased KCC2 but increased NKCC1 expression                                          |
| Petit 2015 (132)  | Stress model E9-E20    | Behavior PND 28                                                                  | PNS E increased anxiety in female pups                                                     |
| Bennett 2015 (133) | Pregnant guinea pigs   | Synaptic transmission: Nr1, Grin2A, Grin2B                                      | Overexpression Dlg4 in amygdala                                                            |
| Skelin 2015 (135) | Pregnant rats          | Myelin basic protein (MBP), glial fibrillary acidic protein (GFAP)                | Reduction in MBP and GFAP in CA1 region HPC                                                |
| Goelman 2014 (134) | Ladostigil L, a mono-amine oxidase inhibitor ± stress | Monoamine oxidase levels Rs fMRI                                                  | Ladostigil inhibited MAO A & B by 45–50%                                                  |
| Ehrlich 2015 (136) | Pregnant rats          | Electrophysiology — PND 10, 14, 17, 20, 28 and 60                               | PNS E reduced amygdala neuron excitability across all days                                 |
| Barzegar 2015 (137) | PNSE E17-20            | Behavior — PND 60                                                                | PNS E neurons had more hyperpolarized resting membrane potential and produced fewer action potentials |
| Negron-Oyarzo 2015 (138) | Noise stress          | Behavior at 1–2 mo                                                                | PNS E showed decreased functional connectivity between neuronal discharge in medial PFC and hippocampal sharp-wave ripples |
| Inflammation     | Preclinical prenatal immune activation model | Expression serotonin 5-HT(2A) and metabotropic glutamate 2 (mGlu2) receptors | Prenatal immune activation increased 5-HT(2A) and decreased mGlu2 expression in frontal cortex |
| Holloway 2013 (139) | Behavior              |                                                                                | Pattern of expression associated with behavioral changes                                    |

#### Brain function and connectivity

| Author/year      | Model                  | Protocol—fetuses                                                                 | Outcome                                                                                   |
|------------------|------------------------|----------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------|
| Bennett 2015 (133) | Pregnant guinea pigs   | Immunohistochemistry, RT-PCR PND 21                                              | Reduction in MBP and GFAP in CA1 region HPC                                                |
| Bennett 2015 (133) | Pregnant guinea pigs   | Myelin basic protein (MBP), glial fibrillary acidic protein (GFAP)                | Reduction in MBP and GFAP in CA1 region HPC                                                |
| Goelman 2014 (134) | Ladostigil L, a mono-amine oxidase inhibitor ± stress | Monoamine oxidase levels Rs fMRI                                                  | Ladostigil inhibited MAO A & B by 45–50%                                                  |
| Skelin 2015 (135) | Pregnant rats          | Unilateral field potential recording power (FP)                                    | FP power lower in medial PFC, amygdala, HPC and striatum in MGPNS pups                    |
| Ehrlich 2015 (136) | Pregnant rats          | Electrophysiology — PND 10, 14, 17, 20, 28 and 60                               | PNS E reduced amygdala neuron excitability across all days                                 |
| Barzegar 2015 (137) | PNSE E17-20            | Behavior — PND 60                                                                | PNS E neurons had more hyperpolarized resting membrane potential and produced fewer action potentials |
| Negron-Oyarzo 2015 (138) | Noise stress          | Behavior at 1–2 mo                                                                | PNS E showed decreased functional connectivity between neuronal discharge in medial PFC and hippocampal sharp-wave ripples |
| Inflammation     | Preclinical prenatal immune activation model | Expression serotonin 5-HT(2A) and metabotropic glutamate 2 (mGlu2) receptors | Prenatal immune activation increased 5-HT(2A) and decreased mGlu2 expression in frontal cortex |
| Holloway 2013 (139) | Behavior              |                                                                                | Pattern of expression associated with behavioral changes                                    |

#### Stress exposure

| Author/year      | Model                  | Protocol—fetuses                                                                 | Outcome                                                                                   |
|------------------|------------------------|----------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------|
| Bennett 2015 (133) | Pregnant guinea pigs   | Immunohistochemistry, RT-PCR PND 21                                              | Reduction in MBP and GFAP in CA1 region HPC                                                |
| Bennett 2015 (133) | Pregnant guinea pigs   | Myelin basic protein (MBP), glial fibrillary acidic protein (GFAP)                | Reduction in MBP and GFAP in CA1 region HPC                                                |
| Goelman 2014 (134) | Ladostigil L, a mono-amine oxidase inhibitor ± stress | Monoamine oxidase levels Rs fMRI                                                  | Ladostigil inhibited MAO A & B by 45–50%                                                  |
| Skelin 2015 (135) | Pregnant rats          | Unilateral field potential recording power (FP)                                    | FP power lower in medial PFC, amygdala, HPC and striatum in MGPNS pups                    |
| Ehrlich 2015 (136) | Pregnant rats          | Electrophysiology — PND 10, 14, 17, 20, 28 and 60                               | PNS E reduced amygdala neuron excitability across all days                                 |
| Barzegar 2015 (137) | PNSE E17-20            | Behavior — PND 60                                                                | PNS E neurons had more hyperpolarized resting membrane potential and produced fewer action potentials |
| Negron-Oyarzo 2015 (138) | Noise stress          | Behavior at 1–2 mo                                                                | PNS E showed decreased functional connectivity between neuronal discharge in medial PFC and hippocampal sharp-wave ripples |
| Inflammation     | Preclinical prenatal immune activation model | Expression serotonin 5-HT(2A) and metabotropic glutamate 2 (mGlu2) receptors | Prenatal immune activation increased 5-HT(2A) and decreased mGlu2 expression in frontal cortex |
| Holloway 2013 (139) | Behavior              |                                                                                | Pattern of expression associated with behavioral changes                                    |
### Table 3. Prenatal stress and the connectome: clinical data

| Author/year | Number | Risk factors/time | Age at scan | Outcome | Results |
|-------------|--------|-------------------|-------------|---------|---------|
| **Neonates** | | | | | |
| Rifkin-Graboi 2013 (24) | 157 | EPDS at 26 wk GA | 6–14 d | dMRI – amygdala | Lower FA ($P = 0.009$) but not volume in R amygdala in infants with high prenatal stress compared to low-normal stress |
| Qiu 2013 (27) | 175 | STAI at 26 wkGA | All at birth 35 wk/repeat scans at 6 mo | Hippocampal volume and growth trajectory | No influence of maternal anxiety on hippocampal volumes at birth |
| **Rifkin-Graboi 2015 (25)** | 54 | STAI at 26 wkGA | 5–17 d | dMRI | High anxiety group – reduced FA in R insula, middle occipital, inf temporal, angular gyrus, uncinate, posterior cingulate, dorsolateral prefrontal, inferior frontal region, cerebellum and inferior fronto-occipital fasciculus; also bilat superior and L postcentral regions |
| Qiu 2015 (26) | 24 | EPDS at 26 wk GA | 6 mo | fMRI – amygdala connectivity | Neonates with high prenatal stress had greater connectivity of amygdala with L temporal cortex, insula, bilat ACC, medial orbitofrontal ventromedial prefrontal cortices |
| **Scheinost 2016 (82)** | 26 | Retrospective review of maternal chart for prenatal stress as documented by diagnosis of maternatal depression and/or anxiety | Term equivalent age (35–40 wk PMA) | fMRI – amygdala connectivity | Preterm neonates with high prenatal stress had reduced connectivity of amygdala to subcortical regions, including the thalamus. |
| **Childhood** | | | | | |
| Buss 2010 (83) | 35 | Pregnancy anxiety scale administered at 19, 25, and 31 wk GA | 6–10 y | Voxel-based morphometry | Anxiety at 19 wk GA associated with decreased gray matter in prefrontal cortex, premotor cortex, medial temporal lobe, lateral temporal cortex, postcentral gyrus and cerebellum extending to the middle occipital gyrus and fusiform gyrus |
| Sarkar 2014 (84) | 22 | Prenatal stress | 7 y | dMRI – FA and perpendicular diffusivity ($D_{perp}$) – Uncinate and a control tract | Prenatal stress correlated positively with R uncinate FA and negatively with R uncinate $D_{perp}$ |
| Sandman 2015 (47) | 81 | Centers for Epidemiologic Studies Depression scale (CESDS) at 19, 25, and 31 wk GA | 6–9 y | MRI cortical thickness | No correlations with control tract |
| **Young adults** | | | | | |
| Favaro 2015 (90) | 35 females | Prenatal stress interview (140) | 14–40 y | Voxel-based morphometry | High prenatal stress associated with decreased gray matter in L medial temporal lobe and both amygdalae |
| | | | | fMRI | Prenatal stress showed positive linear relationship with connectivity between L medial temporal lobe and pregenual cortex |
| | | | | Depression survey | Connectivity between L medial temporal lobe and L medial orbitofrontal cortex partially explained variance in depressive symptoms of offspring |

EPDS, Edinburgh Postnatal Depression Scale.
function in the developing brain. Rifkin-Graboi performed structural MRI and dMRI on 157 nonsedated 6–14-day-old newborns whose mothers participated in the GUSTO study (Growing Up in Singapore Towards Healthy Outcomes), a cohort of Asian women enrolled during the first trimester of pregnancy. Socioeconomic status, prenatal exposures, pregnancy measures, and birth outcomes were recorded, and imaging data were analyzed only for those infants who met the following criteria: (i) gestational age (GA) ≥37 wk, (ii) birth weight (BW) >2,500 g, and (iii) Apgar5 min > 7. The Edinburgh Postnatal Depression Scale and the State Trait Anxiety Inventory (STAI) were administered to all women at 26 wk of pregnancy. Adjusting for household income, maternal age and smoking exposure, postmenstrual age (PMA) at MRI, and BW, Rifkin-Graboi (24) found significantly lower FA but not volume in the right amygdala in infants of mothers with high EDPS scores. This suggests a significant relationship between PNSE and microstructure of the right amygdala, a region associated with stress reactivity and vulnerability for mood disorders.

Similarly, Qiu interrogated the GUSTO cohort to examine the consequences of PNSE to maternal anxiety on neonatal development of the hippocampus, a structure critical for stress regulation (27). Entry criteria for this analysis differed from those of Rifkin-Graboi’s 2013 study, and included both term and late preterm infants who met the following criteria: (i) GA ≥ 35 wk; (ii) BW > 2,000 g; and (iii) Apgar5 min > 9. There were 175 GUSTO infants available for this analysis; 42 underwent repeat scans at age 6 mo, and 35 (83%) had usable data. In Qiu’s analysis, antenatal maternal anxiety did not influence bilateral hippocampal volume at birth, but children of women with increased anxiety during pregnancy showed slower growth of both the left and right hippocampus between birth and age 6 mo. Subsequently, evaluating 21 GUSTO infants with high PNSE (i.e., maternal STAI > 90) and 34 with low PNSE (i.e., maternal STAI < 70), Rifkin-Graboi showed that antenatal anxiety predicted decreases in FA of regions important for cognitive-emotional responses to stress (i.e., right insula and dorsolateral prefrontal cortices (PFC)), sensory processing (right middle occipital cortex), and socio-emotional function (i.e., right angular gyrus, uncinate fasciculus, posterior cingulate, and parahippocampus) at age 5–17 d (25). Of note, infants were eligible for this analysis if met the following criteria: (i) GA ≥ 36 wk; (ii) BW > 2,000 g; and (iii) Apgar5 min > 7.

Finally, Scheinost (82) and Qiu (26) investigated prenatal depression/anxiety exposure and amygdala connectivity using rs-fMRI in preterm neonates at term equivalent age and infants at age 6 mo, respectively. These data showed that, in the neonatal period, the amygdala is functionally connected to subcortical and posterior cortical regions, and, by age 6 mo, is connected to widespread networks subserving emotional regulation, memory, and social cognition. In preterm neonates, Scheinost showed that PNSE reduces amygdalar-thalamic connectivity and is additive to effects of preterm birth. Using 24 GUSTO infants, Qiu showed that infants born to mothers with higher prenatal depressive symptoms had greater rs-fMRI of the amygdala with the left temporal cortex, insula, anterior cingulate (ACC), medial orbitofrontal, and ventromedial PFC. These networks are reported in children and adults with depression, suggesting that rs-fMRI data may foreshadow future neuropsychiatric disease.

Studies During Childhood

Studies of older children also suggest that maternal anxiety is associated with specific changes in brain morphology. Buss evaluated children ages 6–10 y whose mothers had been enrolled in a prospective study of pregnancy at the University of California, Irvine or Cedars Sinai Hospital in Los Angeles, CA, between 1998 and 2002 (83). Families were contacted again in 2007 and invited to participate in a follow-up study of their children to assess the influence of PNSE on brain development. At the time of this report, 35 mother–child dyads had both usable MRI data and complete maternal data. VBM on these children demonstrated that exposure to high maternal stress at 19 wk of gestation correlated with gray matter reductions in the PFC, premotor cortex, medial temporal lobe, lateral temporal cortex, post-central gyrus, and cerebellum extending to the middle occipital and fusiform gyri. Although the numbers are small and assessments of postnatal stress exposure were not included in the authors’ analyses, high pregnancy stress at 25 and 31 wk of gestation was not associated with local reductions in gray matter volume, suggesting the importance of earlier exposure to gestational psychological stress. Similarly, Sarkar performed dMRI studies to assess both FA and perpendicular diffusivity (Dperp) on 22 children ages 6–9 y whose mothers were retrospectively assessed for PNSE when the children were age 17 mo (84). For these children, PNSE was positively correlated with right uncinate FA and negatively with right uncinate Dperp, while PNSE was not associated with control tract properties.

In addition, since reduced cortical volume and thickness have both been associated with a history of depression in adult populations (85,86), Sandman measured cortical thickness in
81 school aged children whose mothers had participated in the longitudinal study described above; (83) all were prospectively evaluated for depression at 19, 25, and 31 wk of gestation (47). Prenatal maternal depression exposure was associated with thinning in the right frontal lobe, and the strongest association was with exposure at 25 wk gestation. Morphological changes were primarily found in the superior, medial orbital, and frontal pole regions of the right PFC, consistent with data in adults with depressive symptomatology (85,86). Further, the significant association between prenatal depression exposure and child externalizing behavior in this cohort of children was mediated by these changes.

Studies During Adulthood
Finally, although MR studies of young adults with early life stress exposures are just beginning to emerge (87–89), Favaro explored the relationship between PNSE, cortical volumes and rs-fMRI in a sample of 35 healthy women aged 14–40 y (90). The sample was composed of volunteers to whose mothers a semi-structured interview assessing stress related events during pregnancy was administered. Subject scores were assigned based on interview data and used for MRI analyses. For these women, greater PNSE was associated with decreased gray matter volume in the left medial temporal lobe and both amygdalae. Strength of PNSE was positively correlated with rs-fMRI at 21–38 wk of gestation, fetuses show evidence of both long-range functional connectivity and the emergence of neural networks across the third trimester, mimicking those in older children and adults (92,93). However, both longitudinal and cross-sectional data are needed to more fully characterize the developmental trajectories of PNSE. To

Table 4. Prenatal stress and the connectome: Endocrine and genetic mechanisms

| Author/year   | Number | Risk factors/time | Age at scan | Outcome                                                                 | Results                                                                 |
|---------------|--------|-------------------|-------------|--------------------------------------------------------------------------|--------------------------------------------------------------------------|
| Hypothalamic-pituitary-adrenal axis |        |                   |             |                                                                          |                                                                          |
| Buss 2012 (33) | 65     | Maternal cortisol at 15, 19, 25, 31, and 37 wk GA | 7 y         | Child amygdala and hippocampal volumes                                    | Higher cortisol levels at 15 wk GA associated with larger R amygdala volume in girls but not in boys |
|               |        |                   |             | Child affective problems                                                  | Higher cortisol levels at 15 wk GA                                       |
| Davis 2013 (141) | 54    | Subjects with and without exposure to antenatal steroid exposure (ANS) | 6–10 y      | MRI – cortical thickness                                                  | Associated with more affective problems in girls but not in boys          |
|               |        |                   |             | Child Behavior Check List (CBCL)                                           |                                                                          |
| Candidate genes |       |                   |             |                                                                          |                                                                          |
| Qiu 2015 (72)  | 146    | Pregnancy anxiety scale administered at 19, 25, and 31 wk GA | Newborn     | Voxel-based morphometry                                                  | Individual COMT SNPs modulated association between antenatal maternal anxiety and prefrontal and parietal cortical thickness |
|               |        |                   |             |                                                                          | Among rs737865-val158met-rs165599 haplotypes, the A-val-G haplotype modulated positive associations of maternal anxiety with cortical thickness in right PFC and right parietal cortex |
|               |        |                   |             |                                                                          | The G-met-A mediates negative associations of anxiety with thickness in bilateral precentral gyrus and prefrontal cortex |
| Epigenetic mechanisms |       |                   |             |                                                                          |                                                                          |
| Chen 2015 (142) | 247   | Maternal anxiety (STAI) at 26 wk of gestation | Newborn     | Regional brain volumes BDNF genotype and methylation status              | Infant brain-derived neurotrophic factor (BDNF) genotype influenced association of prenatal anxiety on both epigenome as well as that between epigenome and right amygdala and left hippocampus volumes |

STAI, State Trait Anxiety Inventory.
begin to address this problem, we performed longitudinal rs-fMRI on 10 typically developing fetuses at 30–32, 34–36 wk PMA and following term delivery. This study was approved by the Yale University Human Investigation Committee, and pregnant women signed consent for the protocol. Because of its documented role in neurobehavioral disorders and alterations in studies of PNSE described above, we interrogated the emergence of amygdala networks during the prenatal period. During the 3rd trimester, left amygdala connectivity is first characterized by local circuitry, then begins to connect to ipsilateral regions in the frontal and temporal lobes, and finally develops connections to the contralateral amygdala (Figure 2). The development of these important cross-hemispheric connections between the right and left amygdala develop during the end of the third trimester and likely increases the vulnerability of this circuitry to PNSE (55).

Timing of Stress Exposure
There is increasing recognition that fetal stress exposure has a particularly pronounced impact during early periods of corticogenesis, commonly known as critical periods in the developing brain. Critical periods refer to epochs characterized by both increasing plasticity and greater vulnerability; thus, these are times when the developing brain may be most easily modified in either favorable or unfavorable directions. Critical periods are thought to be environmentally sensitive, and many authors believe they underlie the developmental origins of neurobehavioral disorders such as ASD.

Typically developing fetuses with PNSE during the middle second and third trimesters of gestation are reported to be at the greatest risk for neurobehavioral disorders (13,52). Reviewing Swedish birth registries, Class examined associations between PNSE in 738,144 offspring born in 1992–2000 for childhood outcomes and 2,155,221 offspring born in 1973–1997 for adult outcomes. Although data for GA are not available, third trimester bereavement stress significantly increased risk of both ASD and attention deficit hyperactivity disorder (55). Similarly, children who had been exposed to tropical storms during gestation months 5–6 or 9–10 had 3.8 times greater risk of developing ASD than children who had been exposed to the same storms, in the same place, but during other months of gestation (52). Duration of maternal stress may also play a role. Analyzing data from 4,682 live births, Latendresse reported that children of mothers with the longest periods of prenatal depression exposure experienced more than seven times increased risk for pervasive developmental disorder when compared to children with no PNSE (53).

In contrast, in the GUSTO study, mothers were assessed for gestational depression and/or anxiety at 26 wk, and MRI measures were correlated with these data (24–27). In addition, Sandman performed depression screening on 82 pregnant mothers at 19, 25, and 31 wk gestation and found that antenatal exposure to maternal depression at 25 wk gestation was significantly correlated with cortical thinning in 24% of the frontal lobes in the offspring (47). Finally, although cortisol levels are not available for subjects in the prior MRI studies, high levels of maternal cortisol at 15 wk (but not 19, 25, 31, or 37 wk) of gestation were associated with amygdala volumetric changes in girls but not in boys (33). Since high levels of cortisol are believed to reprogram the fetal HPA axis and maternal stress has been reported to downregulate 11β-hydroxysteroid dehydrogenase (75), the placental enzyme which metabolizes cortisol (75), future studies of maternal psychological stress during gestation should consider longitudinal assessments of maternal cortisol in tandem with fetal neuroimaging.

Sex Differences in Prenatal Stress Outcomes
The link between PNSE and outcomes may be moderated by fetal sex. The source of sex differences upon early development is unclear but may include placental functioning, exposure to adrenal hormones and testosterone and an assortment of epigenetic mechanisms (94–97). Recent fetal pathways also proposed include sex-dependent responses of the transcriptome (6,98–100), naturally occurring sexually-dimorphic processes mediating neuron-glial interactions (101), and differential responses of target regions in the developing brain (102). Thus, while PNSE may have consequences for both males and females, the specificity of effects may differ. To the best of our knowledge, however, only a single study has reported sex differences in MRI outcome measures. These data suggest that higher cortisol levels at 15 wk of gestation were associated with larger right amygdala volumes and more affective problems in female but not male offspring (33).

MECHANISMS OF PRENATAL STRESS AND THE CONNECTOME
Taken together, published studies of PNSE suggest both proximate and long-lasting influence on the connectome. However, mechanisms of how PNSE alters the developing connectome must be explored. Mechanistic studies have focused on the HPA axis, candidate genes, and epigenetic pathways (see Table 4).

MOVING FORWARD: INVESTIGATION OF THE CLINICAL PROBLEM, CHANGES IN CARE
Converging data suggest that PNSE alters the developing connectome. As noted by Sporns, “The placement of brain connectivity as an intermediate phenotype between environmental exposures and behavior makes it an important target for studies that link networks across levels from behavior to molecules, neurons and emerging networks in the developing brain” (62). To better address the impact of PNSE on the connectome, longitudinal studies of maternal/fetal dyads with and without stress exposure are needed. Such investigations would benefit from repeated assessments of maternal stress in order to identify type, time of onset, and duration of PNSE and correlate these data with sequential imaging. In addition, preconceptional stress may influence offspring outcome, and pregnant women should be surveyed for cumulative stress at the time of study enrollment. Likewise, both genetic variants and epigenetic changes may contribute to outcome in the offspring, and consideration should be made to include these data in PNSE-offspring outcome analyses. Finally, longitudinal
fetal imaging will provide important information about target regions, and developmental trajectory analyses are well suited for interrogation of the developing connectome.

These strategies can be used to detect developmental disturbances of the connectome that may underlie the development of neurobehavioral disorders.

ACKNOWLEDGMENTS
We are indebted to our medical, nursing and research colleagues and the infants and their mothers who agreed to take part in this study. We are also grateful to Michael Labrec, R.T.R., for technical expertise.

STATEMENT OF FINANCIAL SUPPORT
This work was supported by Gates Foundation OPP1119263, Seattle, WA, and National Institutes of Health T32 HD07094, Bethesda, MD.

Disclosures: None of the authors have disclosures.

REFERENCES
1. Dennis EL, Thompson PM. Typical and atypical brain development: a review of neuroimaging studies. Dialogues Clin Neurosci 2013;15:359–84.
2. Di Martino A, Fair DA, Kelly C, et al. Unraveling the miswired connectome: a developmental perspective. Neuron 2014;83:1335–53.
3. Graham AM, Pfeifer JH, Fisher PA, Lin W, Gao W, Fair DA. The potential of infant fMRI research and the study of early life stress as a promising exemplar. Dev Cogn Neurosci 2015;12:12–39.
4. Provencal N, Binder EB. The effects of early life stress on the epigenome: From the womb to adulthood and even before. Exp Neurol 2015;268:10–20.
5. Chen Y, Baram TZ. Toward understanding how early-life stress programs cognitive and emotional brain networks. Neuropsychopharmacol 2016;41:197–206.
6. Bronson SL, Bale TL. Prenatal stress-induced increases in placental inflammation and offspring hyperactivity are male-specific and ameliorated by maternal antinflammatory treatment. Endocrinology 2014;155:2635–46.
7. Constantinof A, Moisiasid SG, Matthews SG. Programming of stress pathways: A transgenerational perspective. J Steroid Biochem Mol Biol 2016;160:175–80.
8. Sinha R. Chronic stress, drug use, and vulnerability to addiction. Ann N Y Acad Sci 2008;1141:105–30.
9. McEwen BS. The neurobiology and neuroendocrinology of stress. Implications for post-traumatic stress disorder from a basic science perspective. Psychiatr Clin North Am 2002;25:469–94, ix.
10. Brown AS. Epidemiologic studies of exposure to prenatal infection and risk of schizophrenia and autism. Dev Neurobiol 2012;62:237–42.
11. Howerton CL, Bale TL. Prenatal programming: at the intersection of maternal stress and immune activation. Horm Behav 2012;62:237–42.
12. Khashan AS, Abel KM, McNamee R, et al. Higher risk of offspring schizophrenia following antenatal maternal exposure to severe adverse life events. Arch Gen Psychiatry 2008;65:146–52.
13. Kinney DK, Munir KM, Crowley DJ, Miller AM. Prenatal stress and risk for autism. Neurosci Biobehav Rev 2008;32:1519–32.
14. Koenig HJ, Kirkpatrick B, Lee P. Glucocorticoid hormones and early brain development in schizophrenia. Neuropsychopharmacology 2002;27:309–18.
15. Li J, Olsen J, Vestergaard M, Obel C. Attention-deficit/hyperactivity disorder in the offspring following prenatal maternal bereavement: a nationwide follow-up study in Denmark. Eur Child Adolesc Psychiatry 2010;19:747–53.
16. Pearson RM, Evans J, Kounali D, et al. Maternal depression during pregnancy and the postnatal period: risks and possible mechanisms for offspring depression at age 18 years. JAMA Psychiatry 2013;70:1312–9.
17. Talge NM, Neal C, Glover V; Early Stress, Translational Research and Prevention Science Network: Fetal and Neonatal Experience on Child and Adolescent Mental Health. Antenatal maternal stress and long-term effects on child neurodevelopment: how and why? J Child Psychol Psychiatry 2007;48:245–61.
40. Mapayi B, Makanjuola RO, Mosaku SK, et al. Impact of intimate partner violence on anxiety and depression amongst women in Ile-Ife, Nigeria. Arch Womens Ment Health 2013;16:11–8.

41. Fisher J, Cabral de Mello M, Patel V, et al. Prevalence and determinants of common perinatal mental disorders in women in low- and lower-middle-income countries: a systematic review. Bull World Health Organ 2012;90:139G–49G.

42. Sawyer A, Ayers S, Smith H. Pre- and postnatal psychological wellbeing in Africa: a systematic review. J Affect Disord 2012;133:17–29.

43. Barthol D, Kriston L, Barkmann C, et al.; International CDS Study Group. Longitudinal course of ante- and postpartum generalized anxiety symptoms and associated factors in West-African women from Ghana and Côte d’Ivoire. J Affect Disord 2016;197:125–33.

44. ACOG Practice Bulletin: Clinical management guidelines for obstetrician-gynecologists number 92, April 2008 (replaces practice bulletin number 87, November 2007). Use of psychiatric medications during pregnancy and lactation. Obstet Gynecol 2008 111:1001–1020.

45. Ko JY, Farr SL, Canfield RL, Yehuda R. The effect of maternal PTSD associated with the World Trade Center attacks and its effect on pregnancy outcome. Obstet Gynecol Surv 2010;65:713–28.

46. Lee AM, Lam SK, Sze Mun Lau SM, Chong CS, Chui HW, Fong DY. Prevalence, course, and risk factors for antenatal anxiety and depression. Obstet Gynecol 2007;110:1102–12.

47. Sandman CA, Buss C, Head K, Davis EP. Fetal exposure to maternal biological stress exerts programming influences on the mother and her fetus. Neuroendocrinology 2012;95:7–21.

48. Suri R, Lin AS, Cohen LS, Altshuler LL. Acute and long-term behavioral impact of preconception stress on the development of dendritic spines and dendritic length in the medial prefrontal cortex. Brain Struct Funct 2015;64:331–41.

49. Lee AM, Lam SK, Sze Mun Lau SM, Chong CS, Chui HW, Fong DY. Prevalence, course, and risk factors for antenatal anxiety and depression. Obstet Gynecol 2007;110:1102–12.

50. Ko JY, Farr SL, Dietz PM, Robbins CL. Depression and treatment among U.S. pregnant and nonpregnant women of reproductive age, 2005-2009. J Womens Health (Larchmt) 2012;21:830–6.

51. Latendresse G, Wong B, Dyer J, Wilson B, Baksh L, Hogue C. Duration of Maternal Stress and Depression: Predictors of Newborn Admission to Neonatal Intensive Care Unit and Postpartum Depression. Nurs Res 2014;75:e1142–52.

52. Li Y, Gonzalez P, Zhang L. Fetal stress and programming of hypoxic/ischemic damage in the human cortex. J Neurosci 2005;25:1142–41.

53. Brand SR, Engel SM, Canfield RL, Yehuda R. The effect of maternal PTSD following in utero trauma exposure on behavior and temperament in the 9-month-old infant. Ann N Y Acad Sci 2006;1071:454–8.

54. Kinney DK, Miller AM, Crowley DJ, Huang E, Gerber E. Autism prevalence following prenatal exposure to hurricanes and tropical storms in Louisiana. J Autism Dev Disord 2008;38:481–8.

55. Latendresse G, Wong B, Dyer J, Wilson B, Baksh L, Hogue C. Duration of Maternal Stress and Depression: Predictors of Newborn Admission to Neonatal Intensive Care Unit and Postpartum Depression. Nurs Res 2015;64:331–41.

56. Sandman CA, Davis EP, Buss C, Glynn LM. Exposure to prenatal psychological stress exerts programming influences on the mother and her fetus. Neuroendocrinology 2012;95:7–21.

57. Scheinost D, Finn ES, Tokoglu E, et al. Sex differences in normal age trajectories of functional brain networks. Hum Brain Mapp 2015;36:524–35.

58. Mora S, Zhang J. Principles of diffusion tensor imaging and its applications to basic neuroscience research. Neuron 2006;51:527–39.

59. Mechelli A, Friston KJ, Frackowiak RS. CT. Structural covariance in the human cortex. J Neurosci 2005;25:8303–10.

60. Evans AC. Networks of anatomical covariance. Neuroimage 2013;80:489–504.

61. Scheinost D, Kwon SH, Lacadie C, Voehr BR, Schneider KC, Papademetris X, Constable RT, Ment LR. Alterations in anatomical covariance in the prematurely born. Cereb Cortex 2016 doi:10.1093/cercor/bhv248.

62. Kolb B, Mychasiuk A, Muhammad A, Li Y, Frost DO, Gibb R. Experience and the developing prefrontal cortex. Proc Natl Acad Sci USA 2012;109 Suppl 2:17186–93.

63. Mariani J, Antoniadis C, Morris MJ. Early-life stress, HPA axis adaptation, and mechanisms contributing to later health outcomes. Front Endocrinol (Lausanne) 2014;5:73.

64. Qiu A, Tuan TA, Ong ML, et al. COMT haplotypes modulate associations of antenatal maternal anxiety and neonatal cortical morphology. Am J Psychiatry 2015;172:163–72.

65. Tsotsi S, Abdulla N, Li C, et al. Fetal DNA methylation of cortisol-related genes and infant neurobehavior at 6 months: The role of antenatal maternal anxiety. Psychoneuroendocrinology 2015;61:35.

66. Bock J, J, Rether K, Gröger N, Xie L, Braun K. Perinatal programming of emotional brain circuits: an integrative view from systems to molecules. Front Neurosci 2014;8:11.

67. 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;37:818–26.

68. 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;37:818–26.

69. Mairesse J, Lesage J, Breton C, et al. Maternal stress alters endocrine function of the feto-placental unit in rats. Am J Physiol Endocrinol Metab 2007;292:E1526–33.

70. Jensen Peña C, Monk C, Champagne FA. Epigenetic effects of prenatal stress on 11β-hydroxysteroid dehydrogenase-2 in the placenta and fetal brain. PLoS One 2012;7:e39791.

71. Lester BM, Padbury JF. Third pathophysiology of prenatal cocaine exposure. Dev Neurosci 2009;31:23–35.

72. Li Y, Gonzalez P, Zhang L. Fetal stress and programming of hypoxic/ischemic-sensitive phenotype in the neonatal brain: mechanisms and possible interventions. Prog Neurobiol 2012;98:145–65.

73. Lussier SJ, Stevens HE. Delays in GABAergic interneuron development and behavioral inhibition after prenatal stress. Dev Neurobiol 2016;76:1078–91.

74. Turkheimer FE, Leech R, Expert P, Lord LD, Vernon AC. The brain’s code and its canonical computational motifs. From sensory cortex to the default mode network: A multi-scale model of brain function in health and disease. Neurosci Biobehav Rev 2015;55:211–22.

75. Scheinost D, Kwon SH, Lacadie C, et al. Prenatal stress alters amygdala functional connectivity in preterm neonates. Neuroimage Clin 2016;12:381–8.

76. Buss C, Davis EP, Muftuler LT, Head K, Sandman CA. High pregnancy anxiety during mid-gestation is associated with decreased gray matter density in 6-9-year-old children. Psychoneuroendocrinology 2010;35:141–53.

77. Sarkar S, Craig MC, Dell’Acqua F, et al. Prenatal stress and limbic-prefrontal white matter microstructure in children aged 6-9 years: a preliminary diffusion tensor imaging study. World J Biol Psychiatry 2014;15:346–52.
85. Peterson BS, Warner V, Bansal R, et al. Cortical thinning in persons at increased familial risk for major depression. Proc Natl Acad Sci USA 2009;106:6273–8.
86. Peterson BS, Weissman MM. A brain-based endophenotype for major depressive disorder. Annu Rev Med 2011;62:461–74.
87. Grant MM, Wood K, Sreenivasan K, et al. Influence of early life stress on intra- and extra-amygdaloid causal connectivity. Neuropsychopharmacology 2015;40:1782–93.
88. Holt NE, Boecker R, Hofm E, et al. The long-term impact of early life poverty on orbitofrontal cortex volume in adulthood: results from a prospective study over 25 years. Neuropsychopharmacology 2015;40:996–1004.
89. Fonzo GA, Ramsawh HI, Flanagan TM, et al. Early life stress and the anxious brain: evidence for a neural mechanism linking childhood emotional maltreatment to anxiety in adulthood. Psychol Med 2016;46:1037–54.
90. Favarro A, Tenconi E, Degortes D, Manara R, Santonastaso P. Neural correlates of prenatal stress in young women. Psychol Med 2015;45:2533–43.
91. Schöpf V, Kasprian G, Brugger PC, Prayer D. Watching the fetal brain at ‘rest’. Int J Dev Neurosci 2012;30:11–7.
92. Anderson AL, Thomason ME. Functional plasticity before the cradle: a review of neural functional imaging in the human fetus. Neurosci Biobehav Rev 2013;37(9 Pt B):2200–32.
93. Thomason ME, Grove LE, Lozon TA Jr, et al. Age-related increases in long-range connectivity in fetal functional neural connectivity networks in utero. Dev Cogn Neurosci 2015;11:96–104.
94. Weinstock M. Sex-dependent changes induced by prenatal stress in cortical and hippocampal morphology and behaviour in rats: an update. Stress 2011;14:690–13.
95. Schaafsma SM, Pfaff DW. Etiologies underlying sex differences in Autism Spectrum Disorders. Front Neuroendocrinol 2014;35:255–71.
96. Lai MC, Lombardo MV, Auyeung B, Baron-Cohen S. Sex/gender differences and autism: setting the scene for future research. J Am Acad Child Adolesc Psychiatry 2015;54:11–24.
97. Romano E, Cosentino L, Laviola G, De Filippis B. Genes and sex hormones interaction in neurodevelopmental disorders. Neurosci Biobehav Rev 2016;67:9–24.
98. Grundwald NJ, Benitez DP, Brunton PJ. Sex-dependent effects of prenatal stress on social memory in rats: a role for differential expression of central vasopressin-1a receptors. J Neuroendocrinol 2015;28:doi:10.1111/jne.12343.
99. Grundwald NJ, Brunton PJ. Prenatal stress programs neuroendocrine stress responses and affective behaviors in second generation rats in a sex-dependent manner. Psychoneuroendocrinology 2015;62:204–16.
100. Mychasiuk R, Gibb R, Kolb B. Prenatal stress produces sexually dimorphic and regionally specific changes in gene expression in hippocampus and frontal cortex of developing rat offspring. Dev Neurosci 2011;33:531–8.
101. Welrington DM, Parikhshan DK, Geschwind DH. Gene expression in human brain implicates sexually dimorphic pathways in autism spectrum disorders. Nat Commun 2016;7:10717.
102. Frahm KA, Peffer ME, Zhang JY, et al. Research resource: the dexametha- sone transcriptome in hypothalamic embryonic neural stem cells. Mol Endocrinol 2016;30:144–54.
103. Ronald A, Pennell CE, Whitehouse AJ. Prenatal maternal stress associated with ADHD and autistic traits in early childhood. Front Psychol 2010;1:223.
104. Grossi E, Veggo F, Narzisi A, Compare A, Muratori F. Pregnancy risk factors in autism: a pilot study with artificial neural networks. Pediatr Res 2016;79:339–47.
105. Gao L, Xi QQ, Wu L, et al. Association between prenatal environmental factors and child autism: a case control study in Tianjin, China. Biomed Environ Sci 2015;28:642–50.
106. Visser JC, Rommel N, Vink L, et al. Narrowly versus broadly defined autism spectrum disorders: differences in pre- and perinatal risk factors. J Autism Dev Disord 2013;43:1505–16.
107. Van den Bergh BR, Mennes M, Oosterlaan J, et al. High antenatal maternal anxiety is related to impulsivity during performance on cognitive tasks in 14- and 15-year-olds. Neurosci Biobehav Rev 2005;29:259–69.
108. van den Bergh BR, Mennes M, Stevens V, et al. ADHD deficit as measured in adolescent boys with a continuous performance task is related to antenatal maternal anxiety. Pediatr Res 2006;59:78–82.
109. Markham JA, Koenig JJ. Prenatal stress: role in psychotic and depressive diseases. Psychopharmacology (Berl) 2011;214:89–106.
110. 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;14:665–76.
111. Laplante DP, Brunet A, Schmitz N, Ciampi A, King S. Project Ice Storm: prenatal maternal stress affects cognitive and linguistic functioning in 5½-year-old children. J Am Acad Child Adolesc Psychiatry 2008;47:1063–72.
112. 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;81:131–48.
113. Yehuda R, Bell A, Bierer LM, Schneider J. Maternal, not paternal, PTSD is related to increased risk for PTSD in offspring of Holocaust survivors. J Psychiatr Res 2008;42:1104–11.
114. Betts KS, Williams GM, Najman JM, Aliati R. Maternal depressive, anxious, and stress symptoms during pregnancy predict internalizing problems in adolescence. Depress Anxiety 2014;31:9–18.
115. Austin MP, Hadzhi-Pavlovic D, Leader L, Saint K, Parker G. Maternal trait anxiety, depression and life event stress in pregnancy: relationships with infant temperament. Early Hum Dev 2005;81:183–90.
116. Blair MM, Glynn LM, Sandman CA, Davis EP. Prenatal maternal anxiety and early childhood temperament. Stress 2011;14:644–51.
117. Salisbury AL, O’Grady KE, Battle CL, et al. The roles of maternal depression, serotonin reuptake inhibitor treatment, and concurrent benzodiazepine use in infant neurobehavioral functioning over the first postnatal month. Am J Psychiatry 2016;173:147–57.
118. Monk C, Feng T, Lee S, Kruppa I, Champagne FA, Tycko B. Distress during pregnancy: epigenetic regulation of placenta glucocorticoid-related genes and fetal neurobehavior. Am J Psychiatry 2016;173:705–13.
119. Davis EP, Glynn LM, Waffarn F, Sandman CA. Prenatal maternal stress programs infant stress regulation. J Child Psychol Psychiatry 2011;52:19–29.
120. Dorrington S, Zammit S, Asher L, Evans J, Heroin J, Lewis G. Perinatal maternal life events and psychotic experiences in children at twelve years in a birth cohort study. Schizophr Res 2014;152:158–63.
121. Betts KS, Williams GM, Najman JM, Aliati R. The relationship between maternal depressive, anxious, and stress symptoms during pregnancy and adult offspring behavioral and emotional problems. Depress Anxiety 2015;32:82–90.
122. Malaspina D, Corcoran C, Kleinhaus KR, et al. Acute maternal stress in pregnancy and schizophrenia in offspring: a cohort prospective study. BMC Psychiatry 2008;8:71.
123. Corcoran C, Perrin M, Harlap S, et al. Incidence of schizophrenia among second-generation immigrants in the Jerusalem perinatal cohort. Schizophr Bull 2009;35:596–602.
124. Jutapakdeeugul N, Afadial S, Polaboon N, Phansuwan-Pujito P, Govitrapong P. Repeated restraint stress and corticosterone injections during late pregnancy alter GAP-43 expression in the hippocampus and prefrontal cortex of rat pups. Int J Dev Neurosci 2010;28:83–90.
125. Afadial S, Polaboon N, Surakul P, Govitrapong P, Jutapakdeeugul N. Prenatal stress alters presynaptic marker proteins in the hippocampus of rat pups. Neurosci Lett 2010;471:223–30.
126. Antenow-Scholker I, Helgert A, Gey C, et al. Adverse effects of antenatal glucocorticoids on cerebral myelination in sheep. Obstet Gynecol 2009;113:142–51.
127. Raschke C, Schmidt S, Schwab M, Jirikowski G. Effects of betamethasone treatment on central myelination in fetal sheep: an electron microscopical study. J Perinatol 2004;24:253–53.
128. Zucchi FC, Yao Y, Ward ID, et al. Maternal stress induces epigenetic signatures of psychiatric and neurological diseases in the offspring. PLoS One 2013;8:e56976.
129. Uchida T, Furukawa T, Iwata S, Yanagawa Y, Fukuda A. Selective loss of parvalbumin-positive GABAergic interneurons in the cerebral cortex of maternally stressed Gadd1-heterozygous mouse offspring. Transl Psychiatry 2014;4:e371.
130. Stevens HE, Su T, Yana-gawa Y, Vaccarino FM. Prenatal stress delays inhibitory neuron progenitor migration in the developing neocortex. Psychoneuroendocrinology 2013;38:509–21.

131. Ehrlich DE, Neigh GN, Bourke CH, et al. Prenatal stress, regardless of concurrent escitalopram treatment, alters behavior and amygdala gene expression of adolescent female rats. Neuropsychopharmacology 2015;40:2135–45.

132. Petit B, Boissy A, Zanella A, et al. Stress during pregnancy alters dendritic spine density and gene expression in the brain of new-born lambs. Behav Brain Res 2015;291:155–63.

133. Bennett GA, Palliser HK, Shaw JC, Walker D, Hirst JJ. Prenatal stress alters hippocampal neuroglia and increases anxiety in childhood. Dev Neurosci 2015;37:533–45.

134. Goelman G, Ilinca R, Zohar I, Weinstock M. Functional connectivity in prenatally stressed rats with and without maternal treatment with ladostigil, a brain-selective monoamine oxidase inhibitor. Eur J Neurosci 2014;40:2734–43.

135. Skelin I, Needham MA, Molina LM, Metz GA, Gruber AJ. Multigenerational prenatal stress increases the coherence of brain signaling among cortico-striatal-limbic circuits in adult rats. Neuroscience 2015;289:270–8.

136. Ehrlich DE, Rainnie DG. Prenatal stress alters the development of socio-emotional behavior and amygdala neuron excitability in rats. Neuropsychopharmacology 2015;40:2135–45.

137. Barzegar M, Sajjadi FS, Talaei SA, Hamidi G, Salami M. Prenatal exposure to noise stress: anxiety, impaired spatial memory, and deteriorated hippocampal plasticity in postnatal life. Hippocampus 2015;25:187–96.

138. Negrón-Oyarzo I, Neira D, Espinoza N, Fuentealba P, Abotitiz F. Prenatal stress produces persistence of remote memory and disrupts functional connectivity in the hippocampal-prefrontal cortex axis. Cereb Cortex 2015;25:3132–43.

139. Holloway T, Moreno JL, Umali A, et al. Prenatal stress induces schizophrenia-like alterations of serotonin 2A and metabotropic glutamate 2 receptors in the adult offspring: role of maternal immune system. J Neurosci 2013;33:1088–98.

140. Rini CK, Dunkel-Schetter C, Wadhwa PD, Sandman CA. Psychological adaptation and birth outcomes: the role of personal resources, stress, and sociocultural context in pregnancy. Health Psychol 1999;18:333–45.

141. Davis EP, Sandman CA, Buss C, Wing DA, Head K. Fetal glucocorticoid exposure is associated with preadolescent brain development. Biol Psychiatry 2013;74:647–55.

142. Chen L, Pan H, Tuan TA, et al.; Gusto Study Group. Brain-derived neurotrophic factor (BDNF) Val66Met polymorphism influences the association of the methylome with maternal anxiety and neonatal brain volumes. Dev Psychopathol 2015;27:137–50.