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Does prenatal stress alter the developing connectome?

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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 underrepresent 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

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Table 1. Disorders and putative prenatal stressors

Disorder	Prenatal stress and representative references
Autism spectrum disorder	Anxiety (13,103)
	Conjugal conflict (104)
	Depression (105,106)
	Maternal bereavement (55)
	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)
	Natural disaster (111)
	Psychosocial stress (60,112)
Depression	Depression (16,48,113)
	PTSD (113)
Internalizing problems	Depression (114)
Neonatal behavioral changes	Anxiety (115,116)
	Depression (48,115,117)
	Natural disasters (49,51)
	Perceived stress scale (118,119)
	PTSD (51)
Pervasive developmental disorder	Depression (53)
Psychosis	Cumulative life experiences (120,121)
	Depression (121)
Schizophrenia	PTSD (122,123)

PTSD, post-traumatic stress disorder.

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).

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

a

High connectivity (r>0.9)

Low connectivity (r>0.1)

Seed connectivity   Independent component analysis (ICA)   Voxel-wise connectivity

b

Region of interest   Tract-based and tractography   Voxel-based
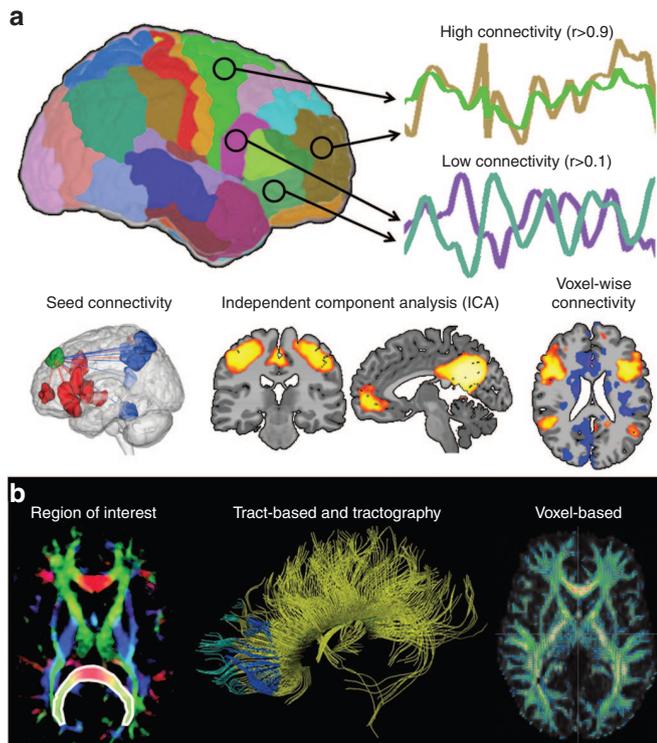
Figure 1. Examples of functional and structural connectivity. (**a**) Functional connectivity. Functional connectivity measures the synchrony or correlation of brain activity between two or more regions of the brain. Common methods include seed connectivity, independent components analysis, and voxel-wise connectivity. Seed-based connectivity measures functional connectivity from a predefined region of interest (ROI, or seed, shown in green) and the rest of the gray matter. Regions of positive or negative functional connectivity are shown as red and blue regions. Independent components analysis is mathematical modeling technique that parcellates the brain into independent spatial components or networks. Example components shown are the motor network and the defualt mode network. Voxel-wise connectivity methods involve correlating the time course of every voxel in the gray matter with the time course of every other voxel in the gray matter. Connectivity for each voxel are often summarized to a single number using network theory to highlight so-called hub regions in the brain. (**b**) Structural connectivity. Structural connectivity measures anatomical white matter connections linking different cortical and sub cortical regions. Common methods include ROI quantification, tract-based and tractography, and voxel-based morphometry. For ROI quantification, average FA across all voxels in *a priori* ROIs (shown in white outline and overlay) is compared across study groups. Tractography is modeling technique used to identifying white matter tracts used in further analyses. In VBM analysis, FA data from all subjects is transformed into a common space and comparison across each voxel of the white matter is performed. (Figure modified with permission, John Wiley & Sons, Hoboken, NJ)

produce a large amount of data (approximately 20,000 seed-connectivity results), seed-connectivity results for each voxel are often summarized to a single number using network theory.

Anatomical connections in the developing brain represent *microstructural connectivity* (66). Diffusion-weighted imaging (dMRI) assesses the diffusion of water along axons and permits visualization of axonal pathways. By modeling the directional diffusion of water as an ellipsoidal shape, or "tensor", at each voxel in the brain, dMRI permits assessment of white matter tracts. The first eigenvector, λ1, describes the direction

of maximal diffusion, while the second and third define diffusivity perpendicular to this principle axis. Radial diffusivity represents the average of λ2 and λ3 and is affected by changes in axon caliber and myelination. Fractional anisotropy (FA) measures the degree to which water diffuses in one direction (along the axon) by computing the ratio of λ1 to λ2 and λ3 and is the most common measure used to assess axonal integrity. High values of FA suggest more highly organized, strongly myelinated tracts.

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 endocrine functions and the "re-programming" of the fetal 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

Table 2. Prenatal stress and the connectome: preclinical data

Author/year	Model	Protocol—fetuses	Outcome
HPA axis function			
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 GAP-43 decreased in PFC at PND 60 Results identical for prenatal stress and corticosterone injection studies
Afadlal 2010 (125)	Pregnant rats Corticosterone 40 mgkg/d E14 – E21	Quantitative immuno-histochemistry Levels of GAP-43, pGAP-43 and synaptophysin in the hippocampus PND 7 and 14	Corticosterone resulted in significant increase of GAP-43 and pGAP-43 in the hippocampus at PND 7 and PND 14 Significant decrease in synaptophysin in hippocampus at same time points
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 Cell counting – mature oligodendroglia Immunohistochemistry – myelin basic protein (MBP)	Within 24 h after treatment, betamethasone reduced number of mature oligodendrocytes and MBP immunoreactivity Maternal and fetal treatment had similar outcomes Loss of MBP immunoreactivity was not reversed 20 d after two treatment courses
Raschke 2008 (127)	Pregnant sheep Betamethasone administered at E 106/147 and E116/147 Lambs delivered preterm at 129/147 d gestation	Electron microscopy	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
Brain structure			
Zucchi 2013 (128)	Prenatal stress	Offspring: brain miRNA Offspring transcription profiles	Stress upregulated miR-219, a suppressor of neural stem cells Stress also upregulated miR-98, an miRNA shown to decrease the cerebral inflammatory response and increase blood brain barrier tightness Transcriptomic changes included genes related to development, axonal guidance and neuropathology
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 PV-positive GABAergic neurons decreased in medial PFC, hippocampus (HPC) and somatosensory cortex of GAD67+/GFP but not wild-type offspring
Stevens 2013 (130)	BrdU at E15 or E12 Pregnant CAD67GFP transgenic mice Restraint stress E12 onwards BrdU E13	Unbiased cell counting Immunohistochemistry *In situ* hybridization PCR – gene expression	Migration of GABAergic progenitors to cortex delayed in PNSE Significant changes in dlx2 and nlx2.1, transcription factors which regulate interneuron migration in PNSE forebrain 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 Behavior at 2–3 mo	Total GABAergic cell number showed altered trajectories in medial PFC and HPC in PNSE mice Parvalbumin neuron proportion in juvenile brain was altered by PNSE but parvalbumin gene expression showed no changes PNSE exhibit behavior changes which correlate with GABAergic populations in medial PFC and HPC

Table 2. Continued on next page

Table 2. Continued

Author/year	Model	Protocol—fetuses	Outcome
Ehrlich 2015 (131)	Pregnant rats	Amygdala GABA interneuron expression Cl- transporters KCC2 and NKCC1	PNSE decreased KCC2 but increased NKCC1 expression
	Stress model E9-E20	Behavior PND 28	PNSE increased anxiety in female pups
Petit 2015 (132)	Pregnant ewes	Offspring expression levels and dendritic morphology PND 1; Dendritic morphology: Dlg4, Rac1, RhoA, Doc2B	Decreased expression Rac1 and NR1 in PFC
	Last third gestation	Synaptic transmission: Nr1, Grin2A, Grin2B	Overexpression Dlg4 in amygdale
	Unpredictable management challenges	HPA axis: Nr3C1	Alterations in spine density and structure in PFC and CA1 region HPC
Bennett 2015 (133)	Pregnant guinea pigs	Immunohistochemistry, RT-PCR PND 21 Myelin basic protein (MBP), glial fibrillary acidic protein (GFAP)	Reduction in MBP and GFAP in CA1 region HPC
	Last third gestation	GABAA receptor subunit	No change GABAA receptor subunit
	Strobe light exposure	Behavior testing PND 18	PNSE pups showed higher anxiety
Brain function and connectivity			
Goelman 2014 (134)	Ladostigil (L, a mono-amine oxidase inhibitor) ± stress	Monoamine oxidase levels Rs fMRI	Ladostigil inhibited MAO A & B by 45–50%
	Pregnant rats		PNSE increased limbic connectivity in the R hemisphere
	L or control - E7–PND21		All connections associated with dopaminergic system (R nucleus accumbens with frontal, cingulate, septum and motor/sensory cortices; R globus pallidus with infra-limbic and dentate gyrus)
	Stress exposure E13-214 groups: PNSE L; PNSE no L; No PNSE – L; no PNSE no L		L prevented stress-induced changes
Skelin 2015 (135)	Pregnant rats	Unilateral field potential recording power (FP)	FP power lower in medial PFC, amygdala, HPC and striatum in MGPNS pups
	PNSE during last third gestation over four generations (multigenerational prenatally stressed, MGPNS)		Coherence of FPs between brain regions high in MGPNS animals among all structures
Ehrlich 2015 (136)	Pregnant rats	Electrophysiology – PND 10, 14, 17, 20, 28 and 60	PNSE reduced amygdala neuron excitability across all days
			PNSE neurons had more hyperpolarized resting membrane potential and produced fewer action potentials
Barzegar 2015 (137)	PNSE E17-20	Behavior – PND 60	PNSE animals decreased socio-emotional behavior
	Pregnant rats	In vivo electrophysiology	Decreased basic synaptic activity in PNSE rats
			Long-term potentiation induction was decreased in CA3-CA1 pathway of hippocampus
Negron-Oyarzo 2015 (138)	Noise stress	Behavior at 1–2 mo	Lower behavioral performance in PNSE rats
	Pregnant mice Prenatal stress model E14-21	Electrophysiology	PNSE showed decreased functional connectivity between neuronal discharge in medial PFC and hippocampal sharp-wave ripples
Inflammation			
Holloway 2013 (139)	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
			Pattern of expression associated with behavioral changes
		Behavior	Similar changes in prenatal stress model

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 wk GA	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; Neonates with maternal anxiety showed slower growth of bilateral hippocampal volumes over first 6 mo compared to neonates with no antenatal maternal anxiety
Rifkin-Graboi 2015 (25)	54	STAI at 26 wk GA; 21 with high scores; 33 with low scores	5–17 d	dMRI	High anxiety group – reduced FA in R insula, middle occipital, inf termporal, 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 maternal 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_{perf}) – Uncinate and a control tract	Prenatal stress correlated positively with R uncinate FA and negatively with R uncinate D_{perf}; No correlations with control tract
Sandman 2015 (47)	81	Centers for Epidemiologic Studies Depression scale (CESDS) at 19, 25, and 31 wk GA	6–9 y	MRI cortical thickness; CBCL	Antenatal exposure to maternal depression at 25 wk GA was associated with cortical thinning in 24% of the frontal lobes, primarily R superior, medial orbital and frontal pole regions of the prefrontal cortex; Association between cortical thinning in R prefrontal region and child externalizing behavior
Young adults					
Favaro 2015 (90)	35 females	Prenatal stress interview (140)	14–40 y	Voxel-based morphometry; fMRI; Depression survey	High prenatal stress associated with decreased gray matter in L medial temporal lobe and both amygdalae; Prenatal stress showed positive linear relationship with connectivity between L medial temporal lobe and pregenual cortex; 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) $Apgar_{5 min}$ > 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) $Apgar_{5 min}$ > 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) $Apgar_{5 min}$ > 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, Qui showed that infants born to mothers with higher prenatal depressive symptoms had greater
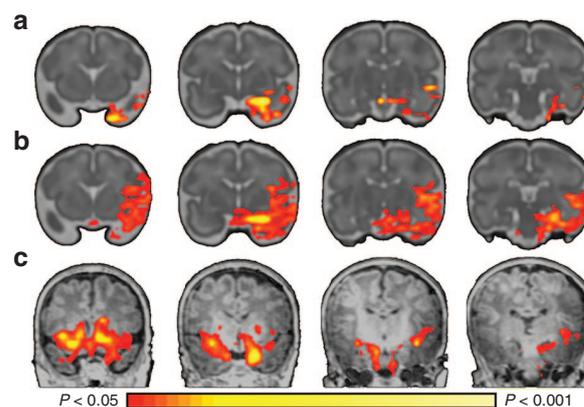
Figure 2. Development of left amygdala functional connectivity during the perinatal period. During the perinatal period, (**a**) left amygdala connectivity is first characterized by a largely local circuitry, (**b**) then begins to connect to ipsilateral regions in the frontal and temporal lobes, and (**c**) finally develops connections to the contralateral amygdala.

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 (D_{perp}) 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 D_{perp}, 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 between the left medial temporal lobe and pre-genual cortex, and connectivity between the left medial temporal lobe and left medial-orbitofrontal cortex partially explained variance in depressive symptoms in this cohort.

EMERGING FACTORS

As studies begin to investigate the impact of PNSE on the connectome, several factors from both preclinical and clinical data have emerged as key considerations for future studies. These factors include defining the normal developmental trajectories of the fetal connectome, the type, timing and duration of PNSE, and the fetal sex. Other factors not addressed within this review include assessing the role of paternal preconception stress and identifying the molecular signatures of PNSE.

Fetal Networks

"Trajectory analysis is central to the assessment of the impact of PNSE on the developing brain." (2) Fetal rs-fMRI is an emerging technology obtaining information about neural network development *in utero* by directly measuring the fetal brain (91). These methods are needed to investigate the prenatal connectome as it develops and pinpoint how and when PNSE alters its development. Using cross-sectional functional connectivity data between 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
					Associated with more affective problems in girls but not in boys
Davis 2013 (141)	54	Subjects with and without exposure to antenatal steroid exposure (ANS)	6–10 y	MRI – cortical thickness	ANS children had bilateral cortical thinning; most significant region was rostral ACC
				Child Behavior Check List (CBCL)	Children with more affective problems had a thinner left rostral ACC
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
				Catechol-O-methyltransferase (COMP) genotypes	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 11 β-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.

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