Title

Prenatal Risk Factors, Developmental Outcomes, and the Human Brain in utero: Maternal BMI and Fetal Brain Functional Connectivity

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Prenatal Risk Factors, Developmental Outcomes, and the Human Brain *in utero*: Maternal BMI and Fetal Brain Functional Connectivity

By

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Abstract

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Mental illness in the US and worldwide is debilitating, costly, and increasing, yet knowledge and treatment for mental disorders lags far behind what is known and what can be done for physical illness. Recent reckoning with this reality has generated new tools and technology, emphasized developmental and translational work across human and animal models, and inspired calls for radical interdisciplinary training approaches and cultural shifts. With these new directions in mind, the current work leverages methodological advances in functional magnetic resonance imaging (fMRI) and dimensional theoretical frameworks to investigate factors in prenatal development that may relate to risk or resilience for the development of mental illness.

This dissertation includes two studies, one assessing the intrauterine influence of elevated maternal weight on fetal brain development, and another, in progress, examining the psychosocial process of maternal-fetal attachment. Prenatal development is a time when the brain is acutely vulnerable to insult and alteration by environmental factors (e.g., toxins, maternal health). It is also a time when prevention and intervention strategies may have the greatest impact in improving developmental outcomes.

Recent research indicates that high maternal body mass index (BMI) during pregnancy is associated with increased risk for numerous physical health, cognitive, and mental health problems in offspring across the lifespan. It is possible that heightened maternal prenatal BMI influences the developing brain even before birth. Study 1 of this dissertation examines this possibility at the level of macrocircuitry in the human fetal brain. Using a data-driven strategy for parcellating the brain into subnetworks, I test whether MRI functional connectivity within or between fetal neural subnetworks varies with maternal prenatal BMI in 109 fetuses between the ages of 26 and 39 weeks.

I found that strength of connectivity between two subnetworks, left insula/inferior frontal gyrus (aIN/IFG) and bilateral prefrontal cortex (PFC), varied with maternal BMI. Global differences in network topography were not observed. The focal effects were localized in regions that will later support behavioral regulation and integrative processes, regions commonly associated with obesity-related deficits. By establishing onset in neural differences prior to birth, this study

supports a model in which maternal BMI-related risk is associated with fetal connectome-level brain organization with implications for offspring long-term cognitive development and mental health.

Study 2 of this dissertation examines maternal-fetal attachment (MFA), a psychosocial process involving maternal behaviors and feelings towards the developing fetus. MFA has been shown to relate to maternal mental health, social support, and physical health habits during pregnancy, as well as later maternal-infant attachment. Although MFA has been studied since the 1980s, there is a lack of consensus around what constitutes MFA and how it should be measured. Study 2 evaluates the psychometric properties (factor structure, invariance) of the most commonly used MFA assessments in two large, diverse samples of American women. A follow-up study is planned to assess the validity and prenatal correlates of the modernized MFA measure. This work aims to provide foundational clarity for future investigation of MFA, an area that holds promise for prenatal intervention and improved outcomes in the many domains associated with attachment.

Finally, closing remarks address future directions and relevance of the present work in the context of current issues in clinical science and public health.

Introduction

Mental illness is a leading cause of disability worldwide, and rates of mental health and substance use disorders are increasing over time in nearly all countries (Patel et al., 2018; Whiteford et al., 2013). According to global health data collected between 1990 and 2014, mental illness accounted for up to 32.4% of disability (total years lived with disability) and up to 13.0% of the overall disease burden (estimated years lost due to disability; Vigo et al., 2016; Vos et al., 2015). For children and youth ages 0-24, mental health and substance use disorders are the first leading cause of disability, and in high-income countries they are also the leading cause of overall disease burden (Erskine et al., 2015). Economically speaking, summaries of data from the US Centers for Disease Control (CDC) showed that the cost of mental illness was $300 billion in 2002 for adults alone, and for children the cost was $247 billion in the 2010s (Perou et al., 2013; Reeves et al., 2011; Younger, 2016). Globally, mental health and cardiovascular diseases are the largest contributors to the global economic health burden, with the $2.5 trillion cost of global mental illness in 2010 expected to inflate to $6.0 trillion by 2030 (Bloom et al., 2012; Trautmann et al., 2016). These estimates do not include costs outside of the healthcare system, such as legal costs associated with substance use illnesses. The estimates also do not account for the alarming and disruptive viral pandemic occurring in 2020, which is currently straining mental health and likely to have long-term psychological consequences for both adults and children (Adhanom Ghebreyesus, 2020; Fegert et al., 2020). It is clear that the impact of mental illness on global health and economies is immense, and growing, yet knowledge and treatment of mental health problems lag far behind what we know and are able to do for physical health conditions (Insel & Gogtay, 2014; Levenson, 2017a; Patel et al., 2018).

The discussion centering around addressing the "…slow (some would say glacial) pace of progress in reducing [the mental health] burden" has intensified in recent years, with multiple solutions being offered (Levenson, 2017a, p. 12). New tools and technology, improved methodologies for clinical trials, better dimensional and multi-modal research paradigms, translational work across human and animal models, interdisciplinary training approaches, and cultural shifts are just a few of the ways future clinicians and scientists will ameliorate the global mental health burden (Casey et al., 2014; Holmes et al., 2018; Insel et al., 2010; Levenson, 2017a, 2017b; Milton & Holmes, 2018).

The present work tackles questions about mental illness and public heath with these approaches in mind. This dissertation comprises two studies, one completed and one in progress.

Study 1 leverages recent methodological advances in functional magnetic resonance imaging (fMRI), dimensional theoretical frameworks for investigating developmental origins and neural mechanisms of mental illness, and insights at the intersection of neuroscience, clinical psychology, and public health. It focuses on effects of maternal obesity during pregnancy on fetal neural development *in utero*. Specifically, functional organization of the developing fetal brain will be assessed at multiple levels of organization (global, modular, subnetwork, and focal/local) for associations with maternal body mass index (BMI). The theoretical framework for the present research is derived primarily from two fields of study: (a) the Developmental Origins of Health and Disease (DOHaD) paradigm, and (b) connectomics.

A second study, to be completed, will examine the psychosocial process of maternal-fetal attachment (MFA), providing insight into another domain and level of analysis in an overlapping sample of mothers and fetuses. Historical context and rationale will be provided in support of Study 2, which will update the Maternal-Fetal Attachment Scale (MFAS; Cranley, 1981) by evaluating its psychometric properties in a diverse, well characterized sample of American women.

After presentation of Studies 1 and 2, final conclusions and closing remarks will include discussion of future directions.

Study One: Literature Review

As just noted, I provide two overarching frameworks for Study 1: (a) The Developmental Origins of Health and Disease (DOHaD) paradigm (Barker et al., 1989; Barker, 1995; Gluckman & Hanson, 2006), which has proven effective in advancing knowledge of physical health problems, is in line with mental health research priorities moving toward earlier periods of development, and is well suited for supporting dimensional and translational research; and (b) connectomics, the study of the complex organization of the brain that facilitates neuronal communication, coordination, and integration.

DOHaD

The basic premise of the DOHaD approach is that early phenotypes such as low birth weight are correlated with prenatal conditions that may elicit biological programming, which operates to shape the structure and function of organs for optimal performance in the fetal environment (Swanson & Wadhwa, 2008, p. 1009).

The notion that adult chronic illness is related to aspects of prenatal development arose from a series of studies by Barker and colleagues describing associations between birth size and adult coronary heart disease (Barker, 1995, 2007; Gluckman & Hanson, 2006). By the early 2000s, there was converging evidence that prenatal factors could influence later noncommunicable chronic illness. Small size at birth was joined by maternal smoking, infection, and obesity in predicting increased risk for a range of chronic medical problems, including diabetes mellitus (type 2), osteoporosis, polycystic ovarian syndrome, hypertension, and stroke (Gluckman & Hanson, 2004; Hanson & Green, 2019).

With respect to mental health, some of the first research studies to describe associations between early programming and latent developmental problems were the Romanian orphan study and ADHD-related work by Swanson and colleagues (Swanson & Wadhwa, 2008; Wadhwa, 2009). Rutter and O'Connor (2004) first observed an association between profound deprivation in infancy and cognitive impairment at age 6 in infants who were raised in neglectful institutions and later adopted, compared to adoptees who did not experience severe deprivation (Rutter & O'Connor, 2004). The authors hypothesized that biological programming related to undernutrition and social neglect underpinned the observed association between neglect and cognitive deficits. Swanson and colleagues (2007) aimed to understand the etiology of ADHD and reviewed evidence

for (1) genetic causes of ADHD (dopamine-related genes, DRD4 and DAT); (2) environmental causes (maternal smoking, lead, and low birthweight); and, crucially, (3) the small handful of gene-environment interaction studies that existed at the time (Nigg, 2016; Swanson et al., 2007). The authors argued that gene-environment interaction hypotheses had the strongest empirical support, though such mechanisms were only just starting to be investigated in ADHD (e.g., epigenetic mechanisms; Mill & Petronis, 2008). This work set the stage for exploration of the conditions in early development that predicted later adverse developmental outcomes, as well as the discovery that much of psychopathology, including neurodevelopmental, affective, social, and psychotic disorders, has intrauterine etiologies (Glover et al., 2018; Monk et al., 2019; Nigg, 2016; Van den Bergh et al., 2017). How do prenatal factors, such as maternal smoking or exposure to toxins like lead, program the fetus to have increased risk for problems like ADHD in adulthood?

Early ideas about the mechanisms underlying DOHaD associations included the "thrifty genotype" (Hales & Barker, 1992) and "predictive adaptive response" (Gluckman et al., 2010), similar ideas that adaptive shifts during fetal development anticipate the postnatal environment and adjust the fetal phenotype to maximize potential for immediate and future success in that environment. The thrifty genotype/phenotype framework has been used to describe associations between prenatal conditions like maternal obesity or stress and increased prevalence of mental health disorders in offspring (Garcia-Rizo et al., 2015; Hubbeling, 2015). A compelling mechanism by which the fetus is "thrifty," or programmed, is epigenetic modulation, the process by which environmental factors alter the fetal phenotype beyond what is programmed by the genetic code. Commonly studied epigenetic mechanisms include histone modification, DNA methylation, and RNA signaling (O'Donnell & Meaney, 2020). These mechanisms are at play in the brain and have been observed in preclinical and human studies to have a role in linking maternal prenatal factors like stress with a number of neurobehavioral deficits and mental health disorders in offspring (Kundakovic & Jaric, 2017).

Overall, the DOHaD paradigm provides an ideal framework for characterizing prenatal conditions that are associated with psychopathology and identifying underlying neural pathways by which the fetal brain can be programmed by various influences (Nigg, 2016).

Connectomics

One way of characterizing the developmental origins of mental illness may be to elucidate prenatal risk-related alterations in the fetal connectome.

The connectome encompasses both anatomical and functional properties of the brain's neural network system (Sporns, 2013). The study of connectomics aims to quantify and visualize connectome organizational properties in order to understand neural functional features from micro-scale (e.g., cellular interactions) to macro-scale (e.g., global topography; van den Heuvel & Sporns, 2019). It has been a popular and productive field in the past 15 years, partly because of the simplicity and generalizability of graph theory, the statistical workhorse of connectomics (Fornito et al., 2016). Broadly, graph theory defines a network of brain regions and connections as a set of nodes and edges. The edges represent associations between nodes, gathered into an association matrix that includes all pairwise associations between nodes. The matrix is thresholded to create a binary adjacency matrix that keeps only the nodes and edges that show a certain level

of association. This solution is compared to a population of random networks using non-parametric significance testing (Bullmore & Sporns, 2009).

Graph theoretical approaches are amenable to analogy (e.g., to computers, airports and flight patterns), easy to depict visually, and simple enough for researchers from biological and social sciences to apply to many systems and types of data without substantial training in mathematics or quantitative fields, all of which facilitates critical translational science (Bullmore & Sporns, 2009; Fornito et al., 2016; van den Heuvel et al., 2016). In addition to these desirable characteristics, connectomics has proved valuable in mapping trajectories of structural and functional brain development across the lifespan (Cao et al., 2017; Cui et al., 2020; Grayson & Fair, 2017) and illuminating the connectomic underpinnings of neurological and psychiatric disorders (de Lange et al., 2019; Griffa et al., 2013; van den Heuvel & Sporns, 2019). Recent advances include applying connectomic analyses to fetal brain data, expanding understanding of neurodevelopmental processes at this stage of development, and opening the possibility of exploring connectomic perturbations that occur before birth.

Development of the Fetal Connectome

The prenatal period is a time of heightened vulnerability in large part due to incredibly rapid neuronal growth, migration, specialization, and organization (Kang et al., 2011). From the third week of gestation to the start of the second trimester, billions of neurons proliferate, developing at a rate of 250,000 neurons per minute by roughly the seventh week of gestation (van den Heuvel & Thomason, 2016). By mid-gestation, around 20 weeks, neuronal migration is largely completed and the density of synapses begins to increase steadily, starting to form network circuitry (Collin & van den Heuvel, 2013; Luhmann et al., 2016; Tau & Peterson, 2010). Primitive forms of functional networks appear to be present from mid-gestation, including an early form of the default mode network (Anderson & Thomason, 2013; Jakab et al., 2014; Thomason et al., 2013). By the third trimester, the basic structural foundation for neural networks is laid and precursors of primary sensory, motor, and default mode networks, sometimes termed "proto-networks," can be identified (Doria et al., 2010; Fransson et al., 2007; Hoff et al., 2013; Smyser et al., 2010; Turk et al., 2019). Across the late second and third trimesters, fetal brain functional networks develop to look increasingly familiar, overlapping with adult brain network maps by 61% (Turk et al., 2019; van den Heuvel et al., 2018).

Research in the last half decade has radically advanced the understanding of overarching organizational properties of fetal functional connectome development. We now know that connectivity develops and strengthens along posterior-to-anterior and medial-to-lateral gradients, with frontal lobe and lateral regions developing later (Thomason et al., 2015). Global metrics of connectivity show a shift from local connections to long-range connections that increase linearly with advancing gestational age (Thomason et al., 2015). In addition, network modularity decreases and efficiency increases with age (Thomason et al., 2014). Networks supporting primary sensory systems develop before higher-order networks in association cortex (Cao et al., 2017; Hoff et al., 2013). A recent study by Turk and colleagues (2019) showed that functional hubs, the most densely connected areas, are located on the medial aspects of the insular and frontal lobes and in somatosensory regions (Turk et al., 2019). These findings extend existing literature that has mapped the human connectome from neonates to adults (Gao et al., 2015, 2016; Li et al., 2019;

Ouyang et al., 2019; Song et al., 2017; Zuo et al., 2017), providing the requisite foundation for comparing typical connectome development to patterns of dysconnectivity that originate before birth and may affect functioning across the life span.

Neural network dysconnectivity underpins nearly every major form of psychopathology (Di Martino et al., 2014; Menon, 2011), and researchers are moving beyond diagnostic-specific neural signatures of mental illness to dimensional approaches (Insel et al., 2010; van den Heuvel & Sporns, 2019). Connectomics offers new methods for examining and understanding the neural properties that underlie cognitive, affective, and behavioral dysfunction across various mental illnesses. One idea is to establish a cross-disorder "landscape" of connectomic alterations that are mapped according to properties of neural wiring and dimensions of functioning (van den Heuvel & Sporns, 2019). An appealing consequence of this approach is that it would support precision medicine. Individual patient neuroimaging assessments could be compared to typical and atypical connectomic charts to inform diagnostic and treatment decisions (Insel, 2014; Turk et al., 2019). The functional dysconnectivity patterns that populate the cross-disorder landscape are not yet known, but there is a foundation of studies examining functional connectomic signatures of single psychological or neurological disorders (for review see van den Heuvel & Sporns, 2019). Another way of using connectomics to explore the neural circuitry underlying psychopathology is to perform longitudinal studies that explore early disruption of network development in relation to later neurodevelopmental problems (de Lange et al., 2019; Jakab, 2019; van den Heuvel & Sporns, 2019). Although this approach is also relatively new, Thomason and colleagues (2018) have demonstrated that differences in fetal brain functional connectivity are associated with infant motor outcomes, and fetal sex modulates how FC relates to infant motor performance (Thomason et al., 2018). Such findings indicate that differences in neural connectivity patterns before birth are correlated with child developmental outcomes, and connectivity alterations can be moderated by risk factors (e.g., male sex) to determine whether or not differences emerge in child functional outcomes.

Taking together the connectomic and DOHaD approaches discussed here, the present work employs a theoretical framework wherein prenatal environmental risk factors may affect early connectivity development, with the potential for subsequent connectomic, behavioral, and mental health outcomes to be negatively impacted. I examine associations in the critical first stage of this process, between maternal prenatal risks (e.g., obesity) and fetal connectomic development. Findings from studies like this should promote opportunities for early risk identification and guidance for treatment.

Maternal obesity and fetal brain functional network organization

The public health concerns related to obesity are significant, and its prevalence has reached pandemic levels (Swinburn et al., 2019; WHO, 2015). Intervention is complicated by the fact that obesity etiology and lifetime prevalence are related to systemic factors that maintain obesity at large scale (e.g., food availability and cost; Swinburn et al., 2019). Given high prevalence of obesity and minimal efficacy of intervention, the risk for obesity-related neurodevelopmental problems in the next generation is also increased. One area where there may be some traction in addressing these challenges is understanding the developmental origins and transmission of obesity-related risk during prenatal brain development.

Obesity is on the rise in the US and worldwide (Bentham et al., 2017) and is associated with numerous negative health outcomes. Among these, obesity is increasingly linked to mental health and cognitive problems, including depression (Milaneschi et al., 2019), anxiety (Rajan & Menon, 2017), and neurodegenerative and neurodevelopmental disorders (Cortese et al., 2016; Whitmer et al., 2008; Zheng et al., 2017), as well as reduced executive functioning (Yang et al., 2018), memory and learning problems (Gunstad et al., 2010), differences in reward response and motivation (Kenny, 2011; Volkow et al., 2011), and mild cognitive impairment (Rochette et al., 2016).

Obesity-related risk can also be transferred from mother to child during the prenatal period. That is, children born to mothers with body mass index (BMI) greater than 30 show increased risk for many of the same problems seen in individuals who are obese (Contu & Hawkes, 2017; Edlow, 2017). Specifically, elevated prenatal BMI has been associated with differences in offspring cognitive performance at age 5 (Basatemur et al., 2013) and affective and social functioning at ages 5 and 6, respectively (Jo et al., 2015; Robinson et al., 2013; Rodriguez, 2010). High prenatal BMI has also been associated with developmental disorders, including attention-deficit/hyperactivity disorder (ADHD) and autism in early and middle childhood (Getz et al., 2016; Sanchez et al., 2018). It is not yet certain precisely when differences emerge, but early neurodevelopmental processes appear sensitive to heightened BMI during pregnancy. Given rising rates of obesity, especially in women of childbearing age (Fisher et al., 2013), and given new knowledge that high prenatal BMI may negatively influence child brain development, an important open question relates to the fetal brain targets of elevated maternal BMI.

Studies in animals with diet-induced obesity during pregnancy provide foundational evidence that maternal obesity affects offspring intrauterine brain development. These studies report differences in neuron proliferation, differentiation, and maturation (Chang et al., 2008; Niculescu & Lupu, 2009; Stachowiak et al., 2013), as well as altered gene expression and DNA methylation patterns (Grissom et al., 2014). Data show that these differences persist in postnatal life (Glendining et al., 2018; Naef et al., 2011; Schmitz et al., 2018; Tozuka et al., 2010; Vucetic et al., 2010) and extend to other domains, including functional and neurochemical processing (Coleman & Parkington, 2016; Sullivan et al., 2010). Brain areas most frequently implicated by prenatal obesity are important for reward processing, higher order cognitive functioning, and mental health, including the prefrontal cortex (Glendining, Fisher, & Jasoni, 2018; Grissom et al., 2014), nucleus accumbens (Naef et al., 2011; Vucetic et al., 2010), and hippocampus (Niculescu & Lupu, 2009; Tozuka et al., 2010). Many of these neurological findings have been linked to alterations in cognitive (e.g., spatial learning), reward, and social behavior, as well as increased anxious and ADHD-like traits (Menting et al., 2019; Sullivan et al., 2014). Taken together, these studies demonstrate that prenatal obesity influences the developing brain before birth, and they provide insight into the specific neurological pathways by which obesity-related transfer of risk may occur.

In contrast to what has been discovered in animal studies, our understanding of the impact of maternal BMI on human intrauterine brain development is limited. Elevated prenatal BMI is a risk factor for neural tube defects (Rasmussen et al., 2008) and congenital anomalies (Vasudevan

et al., 2011), but normative prenatal neurodevelopmental processes sensitive to maternal BMI have yet to be examined.

Studies of human neonates and infants inform hypotheses about prenatal neural variation associated with elevated maternal BMI. A primary example comes from Salzwedel and colleagues (Salzwedel et al., 2019), who observed associations between BMI and functional connectivity (FC) in two-week-old neonates. They report positive associations between BMI and FC in regions critical for cognitive, sensory cue, and motor control processing, and mixed effects in reward processing regions. In a related line of work, Li and colleagues (Li et al., 2016) report decreased FC between dorsal anterior cingulate and prefrontal cortices when mothers had higher body fat percentage early in pregnancy. Salzwedel and colleagues (2019) also performed graph analysis of neonatal functional networks, observing alterations in global degree and efficiency in reward and cognitive control regions in neonates of mothers with high-BMI. Additionally, studies have examined white matter changes related to maternal BMI, demonstrating that high BMI during pregnancy was related to decreased white matter integrity in multiple brain regions within 2-week old neonates (Ou et al., 2015), and that prenatal BMI-related white matter differences can persist into adulthood (Verdejo-Román et al., 2018). These studies provide initial evidence that maternal prenatal BMI may influence intrauterine brain development in humans and implicate sensory, reward, and cognitive control systems as the potential bases of cognitive and behavioral functioning differences in children born to mothers with elevated BMI.

Study aims

The goal of the present study is to assess associations between maternal BMI and human intrauterine brain development. Leveraging recent advances in resting-state functional MRI (rs-fMRI) methodology, my colleagues and I examine functional connectivity across large-scale networks in the human fetal brain. Recent fetal rs-fMRI studies confirm that there are individual differences in prenatal brain network development (Jakab et al., 2014; Wheelock et al., 2019). Such differences relate to exposures (Thomason et al., 2019) and to future preterm delivery (Thomason et al., 2017), and they predict future infant behavior (Thomason et al., 2018). We obtained maternal demographic, health, and fetal rs-fMRI data in 124 mothers and fetuses in order to evaluate BMI-brain associations and potential confounding variables. Based on areas of behavioral impairment associated with high maternal prenatal BMI, we hypothesized that maternal BMI would be associated with variation in fetal FC in the prefrontal cortex, insula, and striatum. We utilized a data-driven strategy for defining subnetworks of the fetal brain followed by enrichment and permutation to determine whether the quantity of nodal connectivity differences within and between subnetworks surpassed the number expected by chance.

Method

Participants

A community sample of 124 pregnant women with singleton pregnancies (age 18-38 years) were recruited during routine obstetrical appointments. Exclusions for participation included presence of suspected fetal central nervous system abnormality as determined by 20-week ultrasound and/or contraindication for MRI (e.g., pacemaker, ferromagnetic material in mother's

body, claustrophobia). Fetuses ranged in age from 20 to 39 weeks gestational age (GA), with GA determined by physician ultrasound examination within one week of MRI scanning. Maternal BMI ranged from 18.6 to 47.8 at MRI scan. Pre-pregnancy BMI data in participants' medical records were limited. Thus, pre-pregnancy BMI was estimated following prior approaches (cf. Dietz et al., 2006), wherein a constant of 1.25 kg was subtracted from maternal weight at the time of MRI then multiplied for weeks >12 by a weight gain rate of 0.4375 kg/week and divided by height (in meters) squared. All participants provided informed written consent, and all study procedures were approved by the Wayne State University Institutional Review Board. Fifteen fetal participants were excluded prior to group level analyses due to (a) low pre-pregnancy BMI (<18.5; n = 6), (b) low birthweight or pre-term birth (n = 6), or (c) GA less than 24 weeks at scan (n = 3), leaving a total of 109 participants with fetal ages ranging from 26.4 to 39.6 weeks. fMRI data from 87 of these participants were recently published in a study of sex-differences in prenatal brain development (Wheelock et al., 2019).

Measures

Maternal BMI was obtained at the time of MRI assessment and calculated in metric units: weight (kg) / height $(m)^2$. In order to account for weight gain over the course of gestation, BMI values used in study analyses were adjusted for GA at scan by computing residual values using the regression BMI ~ GA + error. BMI was treated as a continuous variable, given lack of standardized cut point for defining obesity during pregnancy. Additionally, we collected demographic information (age, race, level of education), physical and mental health measures (physical health habits, depression, anxiety), and birth outcomes (GA at birth, birthweight). Maternal physical health was assessed using an adapted version of the Health Practices Scale (HPS; Jackson, 2006) that measured five domains of health: diet, exercise, medical adherence, substance abuse, and sleep. Descriptions of modifications and psychometric properties of the adapted measure are provided in prior studies by our group (Thomason, Hect, Waller, & Curtain, *under review*). Maternal mental health was assessed using the State-Trait Anxiety Inventory (STAI; Spielberger, 1983), a two-subscale measure of current symptoms and longstanding traits of anxiety (scores range from 40 to 160, delineating no, low, medium, and high anxiety), and the Center for Epidemiological Studies-Depression scale (CES-D; Radloff, 1977), a measure used to screen for depression in the general population in clinical and research settings (scores >16 indicate clinically significant depression symptoms). We calculated Spearman correlations between maternal BMI and health measures and computed descriptive statistics to characterize the demographic make-up and birth outcomes in our sample. We conducted post-hoc analyses to determine if the average overall effect of maternal BMI on fetal FC would be related to maternal education.

Image acquisition

MRI scans were conducted on a Siemens Verio 70 cm open-bore 3T system using a lightweight (500 g) abdominal four-channel Siemens Flex Coil centered approximately at the fetal head. Resting state fMRI data were acquired using a gradient echo planar imaging (EPI) sequence, TR/TE 2000/30 ms, flip angle 80°, 360 frames, slice thickness 4 mm (axial), voxel size 3.4 x 3.4 x 4 mm^3, 12 minutes. When possible, rs-fMRI scans were repeated to attain up to 24 minutes of functional resting state data per participant. The average specific absorption rate (SAR), a measure

of how much heat from radio-frequency energy was absorbed by the tissue (maternal and fetal) during the scan, was 0.20 W/kg (SD = 0.07).

Functional MRI data preprocessing

Data were preprocessed following methods described previously (Thomason et al., 2014, 2017; Thomason et al., 2013). In brief, preprocessing included visual inspection of data to identify segments (time periods) of quiescence, or periods of low fetal movement. All participants included in group level analyses had at least 100 timeframes and lower than 0.53 mm average translational motion. 3D fetal brain masks were created using BrainSuite (Shattuck & Leahy, 2002) on a functional reference frame for each low-motion segment. Masks were binarized and applied to all frames in the segment. Segments were reoriented manually, and SPM8 (http://www.fil.ion.ucl.ac.uk/spm/) was used to realign segments to the mean BOLD volume, resample to 2 mm^3 isotropic voxels, and normalize to a 32-week fetal template (Serag et al., 2012). All realigned, normalized segments were concatenated into one run, realigned to the mean BOLD volume to correct for intrasegment error, and smoothed with a 4 mm fixed-width half-maximum (FWHM) Gaussian kernel. CONN functional connectivity toolbox (v14n; Whitfield-Gabrieli & Nieto-Castanon, 2012) was used to conduct linear detrending, nuisance regression of six head motion parameters and five principal components extracted from the 32-week fetal atlas white matter and CSF mask using aCompCor (Behzadi et al., 2007), and band-pass filtering at 0.008 to 0.09 Hz.

Network analysis

Global network organization was examined to assess a potential relation between maternal BMI and global topological organization of the reconstructed fetal brain networks (Marqués-Iturria et al., 2015). Total network strength (S) was computed as the (non-thresholded) total sum of the brain networks. Next, of the proportional thresholded network, the weighed global clustering-coefficient (C) was computed to assess the level of local connectedness across network nodes (i.e., brain regions). Global efficiency (GE) was computed as a measure of how efficiently the network can exchange information given its layout of connections (Latora & Marchiori, 2001), here computed as the inverse of the harmonic mean of the communication path length in the network. S, C, and GE were computed across the fetal connectome and normalized to S, C, and GE values derived from a population of random networks (1,000 random networks). The relation between network organization and BMI was examined using correlation analysis.

Next, we examined connectional organization at the level of individual subnetworks to assess potential relations between specific subnetworks of network connections and BMI using a Network Based Statistic (NBS) (Verstraete et al., 2014; Zalesky et al., 2010) This NBS analysis provided the opportunity to identify BMI-related subnetworks of connections more closely related to underlying neural architecture than the global organization metrics described above, and included the following steps. First, for each network connection the relation with BMI was computed by means of correlation analysis. Connections showing an effect with a statistical $p < 0.05$ were maintained, and across the network, the largest connected component of BMI-related connections was computed. To evaluate the statistical significance of this subnetwork, the same procedure was repeated for 1,000 random networks, in which BMI labels were permuted and

subnetwork size was similarly stored. The original effect was assigned an NBS subnetwork *p*-level based on the number of random networks that exceeded the original size of the subnetwork of BMI-related connections.

Derivation of fetal brain networks

Fetal brain subnetwork distribution and extent was defined using a data-driven Infomap community detection algorithm (Rosvall & Bergstrom, 2008). In brief, 197 similarly sized, spatially contiguous regions of interest (ROIs) were clustered according to similar patterns of functional connectivity. That is, the average activation time series was computed for each ROI, and the Pearson correlation between the time courses in each ROI pair was computed for the 19,306 possible ROI-ROI pairs. The set of 197 x 197 ROI correlation matrices was thresholded at multiple thresholds (with degrees of sparseness ranging from 1% to 10%, in steps of 0.01%). The Infomap community detection algorithm (Rosvall & Bergstrom, 2008) was applied at each threshold, and the solutions for each threshold were combined using an algorithmic consensus procedure that produced a final, optimal model of fetal brain network structure consisting of 16 functional connectivity networks. The benefit of this widely used parcellation method is that the resulting networks are derived from and preserve the heterogeneity of spatiotemporal patterns in the brain.

Enrichment analysis

Following methods described by Eggebrecht and colleagues (2017), adapted from large-scale genome-wide association studies and similar to prior fMRI approaches (Sripada et al., 2014), enrichment analysis was used to identify significant differences in connectivity within and between fetal brain subnetworks related to maternal BMI residual values, described above. The enrichment approach has been used in recent fetal and infant resting-state studies (Eggebrecht et al., 2017; Marrus et al., 2018; McKinnon et al., 2019; Thomason et al., 2019; Wheelock et al., 2018, 2019). Enrichment uses Spearman rank correlation for each ROI pair and then uses Chi-square test (χ^2, $df = 1$) to determine whether the number of significant connections, thresholded at $p < 0.05$, within each network pair, is greater than what would be expected by chance. This approach identifies network pairs with significantly more BMI-related ROI-ROI connections than would be expected if the overall number of significant BMI-related connections was uniformly distributed across all within- and between-network comparisons. Empirical significance values were determined by random permutation of 10,000 pairings of FC matrices with randomly swapped BMI values (Eggebrecht et al., 2017). Thus, the family-wise error rate was controlled using permutation, and the reported permutation-based *p*-values represented the probability of observing the actual enrichment values in our data at the 5% false-positive level. A schematic of the group level statistical approach is provided in Figure 1. Networks that were significantly enriched for BMI-FC associations were further examined at the level of ROI-ROI pairs to describe positive and negative BMI-FC correlations representing increased and decreased FC associated with higher BMI. All analyses and visualizations were carried out in MATLAB (Release 2016a, Mathworks).

Results

Participant characteristics

The 109 fetuses included in this study were between 26.4 and 39.6 weeks GA at the time of MRI (mean = 33.5, SD = 3.7), born between 34.1 and 42.1 weeks (mean = 39.0, SD = 1.5), and weighed on average 3208.0 g (SD = 517.6) at birth. Average maternal age at MRI was 25.2 years (SD = 4.4). Mothers were 86% African American, 10% Caucasian, and 4% multiracial. Mothers whose highest level of education was a high school diploma or GED constituted 39% of participants, mothers with some college were 36%, those with a 2-year, 4-year, or graduate degree were 6%, and mothers with no diploma or GED made up 17% of the sample. Participant characteristics are summarized in Table 1. BMI at the time of MRI scan (without adjusting for pregnancy) ranged from 22.5 to 47.8 (mean = 33.2, SD = 6.3; Figure 2) and was not significantly correlated with physical health (total composite score, five subscales) or mental health (STAI, CES-D); Spearman correlations ranged from -0.04 to 0.13 (p = 0.20 to 0.72, uncorrected). BMI was also unrelated to motion parameters; Spearman correlations 0.05 to 0.08 (p = 0.39 to 0.60, uncorrected). Neither BMI nor BMI adjusted for pregnancy was correlated with fetal GA; Spearman correlations were -0.13 and -0.08 (p = 0.18 and 0.42), respectively (Table 1).

Network analysis

No specific effects were found examining the relation between BMI and global network organization. S, C, and GE as well as their normalized counterparts did not reveal a significant association with maternal BMI (all $p > 0.05$). NBS analysis also did not reveal one specific subcomponent of maternal BMI-related connections ($p > 0.05$). These findings suggest that global fetal functional neural systems are organized as expected, with BMI effects not specifically tuned to a single subcomponent of functional brain network organization.

Associations between maternal BMI and fetal brain subnetworks

Community detection analysis generated a 16 functional network consensus model (Figure 3) that became the basis for isolating significant relations between maternal prenatal BMI and fetal brain subnetwork connectivity. We observed that maternal BMI was associated with variation in strength of functional connectivity between a bilateral prefrontal cortical network (PFC) and a network encompassing the left anterior insula and inferior frontal gyrus (aIN/IFG) in the fetal brain (Figure 4). Multiple individual connections between pairs of ROIs gave rise to this network-level effect, and in these ROI-ROI pairs the directionality of the association was mixed. That is, both positive and negative associations gave rise to the observed significant cross-network effect of maternal BMI, with the following proportions: 47% and 53%, respectively (Figure 4B). We further observed the spatial organization of the significant connections, noting that positive BMI-FC associations occurred predominantly unilaterally in the left hemisphere (of nine within-hemisphere connections, 67% were positive), whereas negative BMI-FC associations tended to cross the midline (of the six cross-hemisphere connections, 83% were negative) (Figure 4). The latter finding suggests that maternal BMI-related FC effects are associated with increased within-hemispheric connectivity and decreased cross-hemispheric connectivity in prefrontal and left insular cortical regions.

Post-hoc analyses assessing the relation between the average overall BMI-FC effect (including both positive and negative associations) and maternal level of education (as a proxy for socioeconomic status) did not reveal a significant association ($p = 0.22$). Further, we did not observe significant interaction between maternal BMI and education level in relation to fetal FC effects ($p > 0.05$).

Discussion

This study demonstrates an association between maternal BMI and systems-level organization of the developing fetal brain in humans. Using a whole-brain, data-driven approach we discovered maternal BMI-related variation in fetal frontal (prefrontal, IFG) and insular brain regions. These findings support hypotheses that (1) variation in maternal prenatal BMI relates to development of neural systems *in utero* in humans, and that (2) fetal brain regions that show BMI-related connectivity differences are similar to those that will later support processes that are frequently impaired in both individuals with high BMI and those who were exposed to high maternal BMI during prenatal development.

The observed association between fetal prefrontal and insular connectivity and maternal BMI is perhaps not surprising, as these regions have long been of interest in research into behavioral health and obesogenic cognitive effects. The prefrontal cortex plays a central role in cognitive control, including control of eating behavior (Han et al., 2018), and the insula plays a central role in processing food- and appetite-related information (Frank et al., 2013; Rolls, 2006). Alterations in prefrontal structure and function are robustly documented in humans with high BMI (Devoto et al., 2018; García-García et al., 2019; Reinert et al., 2013). Moreover, altered prefrontal brain development is a key finding in studies of prenatal obesity exposure in animals (Rivera et al., 2015; Vucetic et al., 2010) and high BMI exposure in human neonates (X. Li et al., 2016; Salzwedel et al., 2019). The effects we observed in the insular cortices were predominately in the anterior portion, which is regarded as primary gustatory cortex (Rolls, 2006), well-known for integrating cognitive, affective, sensory, and reward-related information (Gogolla, 2017). The anterior insula has been implicated in studies of obesity-related differences in sensory and reward processing (Brooks et al., 2013; Devoto et al., 2018). Given consistent evidence that prefrontal and insular circuits are key neural targets of obesogenic processes, it is notable that in this study we have discovered that differences in these circuits may already be present prior to birth.

There are a number of mechanisms actively being studied in animal models to explore how maternal diet and obesity may influence the developing CNS of the fetus. The present study identifies regions that seem to be relevant for later behavioral development, and animal research provides crucial insight into the pathways by which maternal obesity may influence fetal neural development. Proposed mechanisms include intrauterine exposures to excess nutrients, metabolic hormones, and inflammatory cytokines, which impact neuroendocrine, brain functional and structural, and microbiome development in the fetus (Menting et al., 2019; Sullivan et al., 2014). For example, recent work by Sanguinetti and colleagues (Sanguinetti et al., 2019) showed that maternal high fat diet in a murine model led to changes in the offspring microbiome before weaning, and those changes were later associated with cognitive impairment in the adult animal. Epigenetic mechanisms have also been considered as possible bases of prenatal obesity-related transfer of risk. In particular, obesity-exposed animals have shown epigenetic and neurochemical

alterations in prefrontal and medial temporal brain regions (Glendining et al., 2018; Grissom et al., 2014; Vucetic et al., 2010). For example, a study by Vucetic and colleagues showed that obesity-related epigenetic changes (DNA hypomethylation) in offspring led to alterations in gene expression resulting in up-regulation (increases) of the dopamine reuptake transporter and μ-opioid receptor in the prefrontal cortex, both of which are neurochemical systems critically involved in regulating the intake of palatable foods (Grissom et al., 2014; Vucetic et al., 2010). Another study by Glendining and colleagues revealed altered epigenetic markers in several areas, including the prefrontal cortex in which they observed downregulation of a gene (GADD45B) associated with cell growth, synaptic plasticity, and response to environmental stresses (Glendining et al., 2018). Importantly, these studies in animals have linked maternal obesity-related epigenetic and neurochemical differences to behavioral variation in offspring, including preference for sugar and fat (Vucetic et al., 2010) and increased impulsivity (Grissom et al., 2014). Overall, studies in animals provide a basis for future consideration of the mechanistic pathways that might underpin the association we have observed in humans between maternal prenatal BMI and prefrontal/insular brain development *in utero*.

Maternal BMI-related risk was associated with both positive and negative differences in fetal brain functional connectivity. Notably, positive BMI-FC associations were predominately within-hemisphere connections, whereas negative BMI-FC associations were predominately cross-hemisphere connections (Figure 4). This is preliminary evidence that maternal BMI-related FC effects are associated with increased within-hemisphere connectivity and decreased cross-hemisphere connectivity in prefrontal and left insular cortical regions. Prior research has shown that cross-hemisphere and longer-range connectivity in the fetal brain *increases* across the gestational stages tested in the present study (second/third trimester) (Jakab et al., 2014; Thomason et al., 2013). Thus, the observation of less robust cross-hemisphere connectivity in fetuses of mothers with higher BMI may reflect less mature functional organization. Future research will be needed to test this possibility in a longitudinal framework and to link this potential mechanism to future neurobehavioral health and development.

The left laterality of our insula/IFG connectivity effects is congruent with precedent in the adult literature (Brooks et al., 2013; Devoto et al., 2018; Wijngaarden et al., 2015). For example, Devoto and colleagues showed that the left insula responds to food-related visual stimuli and is differentially engaged during hunger states in individuals with high compared to healthy BMI (Devoto et al., 2018; Wijngaarden et al., 2015). In healthy weight adults, Jakab and colleagues found that structural connections of the left anterior insula are more extensive than the right, particularly with prefrontal and frontal brain regions (Jakab et al., 2012). The authors note that this asymmetry corresponds to putative biomarkers of overeating behavior in adults with obese BMI. Laterality has also been reported in brain development prior to birth. Asymmetries in fetal brain morphometric, microstructural, and functional development are well documented (Clouchoux & Limperopoulos, 2012; Galaburda et al., 1978; Toga & Thompson, 2003). Thus, data from this study of prenatal BMI-related risk raise questions as to the origin of asymmetry differences and whether these could arise from interactions between intrauterine developmental processes and heightened maternal BMI.

In this study, the measure of BMI was derived from assessment at the time of the MRI, correcting for duration of the pregnancy. A limitation of this approach is that measurement of BMI

at different stages of pregnancy has potential to yield different effects (Luzzo et al., 2012). In addition, BMI is a relatively coarse measure and has shown variable accuracy across sex and ethnicity (Gallagher et al., 1996; Sumner et al., 2007). We also expect that maternal body composition, weight and weight gain, and nutritional resources all have potential to impact the developing fetal brain in unique ways. Useful future directions will be to examine weight change over the course of pregnancy, to perform more in-depth assessment of maternal diet, and to examine maternal body composition using techniques such as anthropometry, densitometry, hydrometry, and MRI-based methods, such as Dixon and liver fat content MR imaging (Dixon, 1984; Most et al., 2018). Investigations aimed at improving clinical utility and understanding of how excess weight confers risk will be crucial (e.g., determining thresholds of weight that confer risk, identifying sensitive phases for weight change during pregnancy). With these data it will be possible to begin to map specific physiological or nutritive pathways associated with early human brain development.

There are additional limitations of the present study that warrant consideration. The cross-sectional nature of our study does not permit us to assess how the observed effects map onto postnatal brain and behavioral development. Future longitudinal research will have potential to elucidate developmental processes sensitive to maternal prenatal diet and body composition and identify associated differences in brain and behavioral outcomes. Another methodological challenge is motion, particularly in fetal data. Although our motion threshold is consistent with the fetal literature (e.g., Jakab et al., 2014; Schöpf, Kasprian, Brugger, & Prayer, 2012; Thomason et al., 2013), it is liberal relative to that used in non-fetal resting-state studies. This is an ongoing challenge for the relatively nascent field of fetal imaging (Di Martino et al., 2014). Last, environmental factors such as maternal socioeconomic status, food insecurity, or health behavior have potential to interact with maternal body composition and/or diet to influence fetal brain development. Here, we did not observe an association between fetal FC and maternal level of education; however, this does not eliminate possibility that alternative factors may have contributed to effects observed here. A major goal for future studies will be to examine these associations at a much larger scale to begin to disentangle complex relationships between prenatal contextual programming factors and specific alterations in human fetal neural circuitry.

Important questions also remain regarding the contribution of genetic and postnatal environmental factors to observed associations between prenatal maternal BMI and child developmental outcomes. Overall, existing data indicate that genetic and environmental factors play a prominent role but do not fully account for variation observed in developmental outcomes. Indeed, population studies that cut across socioeconomic strata and population genetics indicate that when genetic and postnatal environmental factors are accounted for, differences related to maternal prenatal diet and body weight persist (Lumey et al., 2011). For example, the offspring of women who conceived and carried during the *Dutch Hunger Winter*, a famine that affected the western Netherlands during World War II, later demonstrated higher rates of depression, schizophrenia spectrum disorders, and antisocial behavior (Hoek, Brown, & Susser, 1998; Neugebauer, Hoek, & Susser, 1999; Stein, Pierik, Verrips, Susser, & Lumey, 2009), greater age-related decline in cognitive ability (de Rooij et al., 2010), and differences in brain morphometry (Hulshoff Pol et al., 2000). This work confirms that atypical maternal body weight and nutrition before birth can increase risk for offspring mental health and cognitive problems over and above genetic and environmental factors. Additionally, it is clear that both low and high maternal health

extremes have potential to influence fetal neurodevelopment, and investigation of differential neural effects, mechanisms, or child outcomes remains an important area for ongoing and future research.

In conclusion, the present study provides evidence that maternal prenatal BMI is associated with variation in functional connectivity in large-scale networks in the fetal brain, specifically in frontal and insular neural circuitry. Given the role of these brain regions in cognitive control and food regulation behavior, as well as in integration of neural connectivity, the present data support a model of risk transfer wherein maternal prenatal BMI relates to fetal brain development with implications for both future body health and neurobehavioral outcomes. Replication and longitudinal research are needed to confirm our findings, to elucidate the significance of lateralized and hemispheric organizational effects, and to determine the ways in which BMI-related changes in fetal brain development relate to later neurodevelopmental and behavioral outcomes. Armed with this information, it may be possible to develop interventions that address prenatal maternal physical health to improve offspring health and cognitive outcomes.

Study Two: Psychometric Evaluation of Maternal-Fetal Attachment Scale (MFAS)

In the interest of interdisciplinary work, investigating multiple levels of analysis, and the potential for clinical intervention, the next set of studies will move from biological programming processes and embrace psychosocial processes, framed generally by classical psychological attachment theory (Bowlby, 1969). In this section, I will introduce the construct of maternal-fetal attachment (MFA), which has been shown to be a predictor of the early bond between mother and child (Alhusen et al., 2013; Doster et al., 2018), the mother's health behavior during pregnancy (Fonagy et al., 1991; Siddiqui & Hägglöf, 2000), and infant developmental outcomes (Alhusen et al., 2012, 2013). I will provide historical context and rationale for evaluating the psychometric properties of the Maternal-Fetal Attachment Scale (MFAS; Cranley, 1981) and explain the methodological approach and overall scope of the project. The data analyses and results will be described in subsequent publications (not included in the present dissertation).

Literature Review

To understand the emergence of the psychological construct of maternal-fetal attachment (MFA), it is helpful to set the stage with some medical history. Over the course of the 20th century, advances in technology and medicine significantly increased the viability of pregnancy in developed countries, including the US. Mother and infant mortality rates decreased, and the primary concern for expecting mothers and families advanced beyond merely surviving pregnancy and childbirth. Additionally, the invention and broad availability of ultrasound by the late 1950s allowed mothers and families to see the fetus and begin to think of it as "baby," living and human. Thus, it became appropriate to consider the emotions, thoughts, and habits a woman developed during her pregnancy in relation to her fetus, and to operationalize this set of maternal experiences in order to assess their relation to maternal and fetal health during pregnancy, birth and later development.

Cranley was the first to develop a measure of MFA, devised through careful review of the extant literature, interviews with clinicians and a group of Lamaze teachers, and edits from nurses, clinicians, and pregnant women. The result was an instrument that was theoretically based and ecologically valid. The literature synthesis drew together ideas from a number of psychological theories at the time. One group suggested that a crucial component of the pregnancy experience was role transition, "reconsideration of maternal self-image and her role as it had been to what it was to become" (Bibring and Valenstein, 1976 as cited in Cranley, 1981, p. 281). Another contribution was Rubin's (1976) four maternal tasks of pregnancy: 1) seeking safe passage for self and child through labor and delivery, 2) insuring acceptance of the child in the family, 3) binding to the unborn child, and 4) learning to give of self (Rubin, 1976). Another idea Cranley considered was the "narcissistic" relationship framework in which pregnancy was a process of "incorporation" of the fetus wherein the mother gradually recognizes it as apart from herself and begins to place some of her mental energy in it (Deutsch, 1945 as cited in Cranley, 1981). Cranley then collected a series of statements that mothers frequently made about themselves and their fetuses in consultation with clinicians and Lamaze instructors.

An initial draft of the resulting instrument was reviewed by five expert medical professionals and a group of pregnant women before going on to statistical validation. The historical context of the development of this scale highlights the extent to which it was derived from consideration of the prevailing theoretical views of the time, clinical experience, and qualitative data from the group the instrument would seek to study. For its time, the scale was a progressive and empirically based tool that allowed scientists and clinicians to conceptualize, quantify, and evaluate the psychosocial processes unfolding over the course of pregnancy. It may be that the enduring influence and widespread use of Cranley's Maternal-Fetal Attachment Scale (MFAS) owes its success in part to the scale-development process, which synthesized theoretical and individual information. At the same time, it is clear from subjective review of the scale and decades of research that the MFAS is due for an upgrade.

The limitations of Cranley's scale have been well documented in terms of both reliability and validity. Cranley reported that the 24-item MFAS had a five-subscale structure and an overall internal reliability of 0.85, but replication of these findings has been mixed (Cranley, 1981). Several research groups have investigated the reliability of the MFAS. They found across studies that the internal consistency for the total scale was similar to Cranley's original report, somewhere between 0.76 and 0.92, but for the five original subscales, alphas ranged from 0.40 to 0.89 (Müller & Ferketich, 1993; Sjögren et al., 2004; Van den Bergh & Simons, 2009). The 'attributing' and 'role-taking' factors were the strongest, with reliability between 0.63-0.84 and 0.68-0.89, respectively; all other subscales are below 0.69 (Müller & Ferketich, 1993; Sjögren et al., 2004; Van den Bergh & Simons, 2009). In addition to the relatively low internal consistency of its subscales, criticisms of the MFAS included lack of operational definition (Mercer et al., 1988) and lack of consideration of maternal feelings regarding the fetus (Condon, 1993). Such criticisms led to the development of alternative instruments for measuring MFA.

Condon (1993) contended that Cranley's MFAS evaluated maternal emotions about the physical state of pregnancy but did not assess feelings and thoughts about the fetus itself (Condon, 1993; Condon & Corkindale, 1997). Condon's view of MFA was based on adult attachment theory, particularly Bretherton's broad view of attachment as an "emotional tie" or "psychological bond"

to a specific object (Bretherton & Waters, 1985). The Maternal Antenatal Attachment Scale (MAAS; Condon, 1993) was developed to address features not measured by Cranley's MFAS and consisted of 19 items focused on maternal thoughts and feelings about the fetus and the developing maternal-fetal bond, ignoring the physical state of pregnancy. The Condon scale has two factors: 1) quality (affective experiences the mother reported) and 2) intensity (amount of time spent thinking about, talking to, dreaming about, or tactilely interacting with fetus). An interesting feature of this scale is that the quality and intensity factors can be oriented as orthogonal continua, resulting in four quadrants: 1) strong/healthy attachment (high quality and high intensity), 2) positive quality of attachment but low preoccupation with fetus due to distraction or avoidance, 3) uninvolved or ambivalently involved, with low preoccupation, and 4) anxious, ambivalent, affectless preoccupation (Condon, 1993; Rossen et al., 2017).

Other MFA measures exist (for review see McNamara et al., 2019), but the two scales above are the most often used (Laxton-Kane & Slade, 2002). They can be combined with other MFA measures to assess different facets of MFA (e.g., Hsu & Chen, 2001; Huang et al., 2004). Adaptations are also plentiful, including the relatively common practice of removing items such as "I feel my body is ugly" (Busonera et al., 2016; Müller & Ferketich, 1993; Sjögren et al., 2004) and translation into other languages (Andrek et al., 2016; Busonera et al., 2016; Chen et al., 2013; Doster et al., 2018; Huang et al., 2004; Narita & Maehara, 1993; Punamäki et al., 2017; Rossen et al., 2017). There is also a paternal-fetal attachment scale (PFAS; (Cranley, 1981; Weaver & Mecca, 1983), and although it is beyond the scope of the present work the curious reader is referred to Brandon et al. (2009, p. 7).

It is evident from the historical account of MFA measurement that there is some disagreement about the definition of maternal-fetal attachment. The field has grappled with this challenge even as understanding of MFA has grown, and several groups have noted that the term "attachment" may not be accurate in the classical sense (Walsh, 2010). Bowlby and Ainsworth describe attachment as the bond between the infant and at least one caregiver that promotes feelings of security/insecurity and the opportunity to safely explore the environment during the earliest stages of development (approx. 0-2 years; Bowlby, 1969; Bretherton, 1992). One contention is that the term "attachment" cannot be applied to prenatal development, because it signifies a reciprocal social interaction, and the fetus is unable to initiate the social overtures inherent to the attachment process (Van den Bergh & Simons, 2009). Yet, the use of other terms, including "bond" and maternal-fetal "relationship," has failed to take hold in the literature, and "attachment" remains the most preferred (Eichhorn, 2012; McNamara et al., 2019). Some researchers point to studies demonstrating prenatal learning and memory for stories, music, voices, and particular languages and contend that it may not be inaccurate to refer to maternal-fetal interactions as "attachment" (Eichhorn, 2012). A related view is that "the mother appears to be 'attaching' to an image of her own creation, not the actual being developing in her womb" (Eichhorn, 2012; p. 51). The field may benefit from a unified nomenclature and conceptualization of the MFA construct. An update to the most frequently used measure, which remains largely unchanged after 40 years, may be a prerequisite for achieving a unified theory of fetal attachment.

Another significant shortcoming of current research using the MFAS is that racial/ethnic minority groups are highly underrepresented in US samples pertaining to this measure. It is critical

that a significant proportion of women of color be included in the analyses that establish the updated MFA instrument, so that it is a valid, generalizable measure of MFA in American women.

Specific Aims

The specific aims of the present study are: 1) to investigate the psychometric properties of the Maternal-Fetal Attachment Scale, including factor structure and measurement invariance, using two large samples of American women; and 2) to make recommendations to the field regarding an upgraded scale to be used in future MFA research.

Method

This project was delayed from March-August 2020 due to the coronavirus pandemic. It was anticipated that data would be available to perform psychometric analysis, but data could not be obtained and analyzed. Thus, an overview of the methodological approach is provided as well as a brief discussion of planned future research directions for investigating scale validity and aspects of prenatal life that are associated with MFA.

Following prior work (Dotterer et al., 2017; Waller et al., 2015), the present study will assess the factor structure of MFA using confirmatory factor analysis (CFA) to test models of two, three, four, and five factor structures (Müller & Ferketich, 1993), as well as potential bifactor models, in two large, diverse samples of American women. In a second step, the best fitting model will be evaluated for measurement invariance across the samples to show that the MFA construct and factor structure solution are similar across different samples. Conceptually, invariance of MFA across two samples of women with different racial/ethnic backgrounds, from different regions of the US, would indicate that MFA and its factor structure as assessed by the modified MFA scale from the first step are likely to generalize to other US samples/women. Items and factors that are invariant across samples will be retained. A future study will examine the validity of the resulting MFA instrument and investigate aspects of prenatal life (e.g., physical health habits, social support) that may be related to MFA.

Participant Sample 1

Sample 1 consists of 248 mother-fetus dyads recruited in Detroit, MI. The racial/ethnic composition of the sample is 37% Black, 36% Latina, 17% White, 2% Asian, 2 % Native American, and 1% multi-racial. All participants provided informed written consent, and all study procedures were approved by the Wayne State University Institutional Review Board. Participants completed self-report questionnaires, including a demographic questionnaire and the maternal-fetal attachment scale (MFAS).

Participant Sample 2

Sample 2 consists of 224 mother-fetus dyads recruited in Providence, RI. The racial/ethnic composition of the sample is 10% Black, 32% Hispanic, 65% White, 1.5% Asian, and 18% multi-racial. All participants provided informed written consent, and all study procedures were IRB

approved. Participants completed questionnaires and interviews, providing demographic and MFAS data.

Measures

Demographic variables including maternal age, gravida para, income, household size/makeup, education, racial/ethnic background, and fetal gestational age at time of assessment were collected.

Maternal-Fetal Attachment Scale (MFAS). MFA was assessed via self-report using the 24-item scale developed by Cranley (1981). Participants responded on a 5-point Likert scale (1 = "absolutely no" to 5 = "absolutely yes") to items such as "I enjoy watching my tummy jiggle as the baby kicks inside" and "I imagine myself taking care of the baby." It is suggested that the MFAS has a five-factor structure, including the following subscales: (1) differentiation of self from fetus, (2) interaction with the fetus, (3) attributing characteristics and intentions to the fetus, (4) giving of self, and (5) role-taking.

Analytic Approach and Hypotheses

First, the factor structure of MFA data will be assessed by CFA in each sample separately. Multiple factor structures have been documented in the literature and will be tested using MFAS data, including two, three, four, and five-factor models. It is also possible that MFA represents a general overall construct with multiple sub-constructs. That is, MFAS data may fit a bifactor model consisting of one global factor and multiple sub-factors. The global factor would relate to all items that fit the model, and sub-factors would involve only items related to that sub-construct. Such a model has not been tested in the literature as far as I know, but the lack of consensus regarding the MFA construct merits testing a bifactor model as an alternative to previous models. CFA will be used, as opposed to exploratory factor analysis (EFA), to allow for comparison of the strengths/weaknesses of proposed models. I hypothesize that a good model fit will be achieved and that similar factor structures will emerge in both samples.

Second, chi-square tests will be used to evaluate invariance of factor structure solutions in both samples (Sass, 2011; Waller et al., 2015). I hypothesize that a majority of MFA factors will show invariance in the best fit model. Factors and/or items from the MFAS that do not show invariance will be dropped. The psychometric properties of the final scale in the overall group (both samples combined) will be reported.

A subsequent set of studies will further examine the validity of the revised MFA scale by investigating associations between MFA and physical health practices, BMI, substance use, mental health (anxiety, depression), social support, and stress.

Overall, this work will provide a contemporary tool for assessing MFA and shed light on the role of this psychological process in maternal and fetal health during pregnancy. MFA measures that assess the behaviors, attitudes/beliefs, and emotions of the mother-fetal relationship will be a crucial for investigations seeking to determine whether or not "attachment" is the appropriate conceptual framework for MFA.

General Discussion, Future Directions, and Concluding Remarks

Insights from the studies presented here have potential to inform prenatal health science, future neuroscience and developmental research, and aspects of women's health. Additionally, in this section I touch upon larger themes, including stigma, conscientious research, empathy and regard for humanity, personal narratives, idiographic methods, and individualized treatment, taking the opportunity to reflect upon common goals, narratives, and concerns in clinical and psychological science.

As a frequent Reader (i.e., grader) for undergraduate psychology courses, I always appreciated that each semester I would encounter a handful of undergraduate papers that would show me something I didn't know before, make connections I hadn't considered, or ignite my curiosity. Recently, I came across an exemplary student paper that challenged previous conclusions about mediators of the association between academic math achievement and race/gender suggesting that black boys had lower achievement scores than girls and children of other racial/ethnic groups (Berry et al., 2011; Thompson & Lewis, 2005). The student wove their personal thoughts and relevant experience into the narrative alongside academic sources, which increased the humanity and concreteness of their conclusions and recommendations for the field. The paper inspired me to explore an unfamiliar literature and to review and re-center my values as a developmental psychologist, teacher, and person.

Personal accounts can strengthen psychological science and uncover truths that were previously obfuscated by bias, stigma, or statistics. I have observed mentors thoughtfully share personal experience in talks, papers, and books (e.g., Hinshaw, 2017) which is in line with research indicating that personal accounts reduce stigma (Corrigan et al., 2018; Scior et al., 2020). Valuing individual-level data is also in line with cultural shifts that have been happening in psychological and clinical science (Holmes et al., 2018; Levenson, 2017a, 2017b). For example, one suggestion to advance public mental health, given underwhelming progress, is to devalue evidence related to group-level symptom reduction because this may not generalize at the individual level (Fisher et al., 2018). That is, "social, existential, and somatic outcome domains" may be more effective targets than symptoms that fall into DSM categories (van Os et al., 2019, p. 88). It is important to recognize that individual and idiographic methods are not new (e.g., Allport, 1962), but these tools are increasingly employed in neuroimaging (e.g., Dubois & Adolphs, 2016; Poldrack et al., 2015) and continue to be valued in clinical science (Barlow & Nock, 2009; Fisher & Boswell, 2016). Although it is rarely emphasized in research-focused training programs, clinical ideography is one way to answer the call for researchers and providers to convene in implementation science and precision medicine to bridge "the unconscionable gap between what we know and what we do" (Hyman, 2012; Insel, 2014). There is a symbiosis between the value of individual data and the power of large sample sizes and population-level research. Thus, in this time of critical self-reflection in mental health research and care, at a time of reflection and social/racial reckoning in the United States, I begin my closing remarks with a personal narrative.

My early work in graduate school examined neural mechanisms underpinning ADHD, which affects 5-11% of children (Visser et al., 2014) and persists into adulthood for 35-78% of childhood-diagnosed individuals (American Psychiatric Association, 2013; Biederman et al., 2010). ADHD is characterized by inattention, disorganization, hyperactivity, and impulsivity

(American Psychiatric Association, 2013), and in adulthood can cause ongoing impairment in social, academic, and occupational functioning (Faraone et al., 2006; Kessler et al., 2006). It has been shown that females with ADHD experience different symptoms and outcomes than their male counterparts. For example, a common finding is that females with ADHD exhibit more problems with inattention, and males with ADHD show more problems with impulse control (Nussbaum, 2012). Young adult women with ADHD have actually shown higher rates of both hyperactive and inattentive symptoms than young men with ADHD, as well as higher impairment in social and daily functioning (Fedele et al., 2012). Finally, females with childhood-diagnosed ADHD are particularly vulnerable to suicide and self-injurious behavior (Hinshaw et al., 2012), peer rejection (Meza et al., 2016), intimate partner violence (Guendelman et al., 2016), elevated BMI and unplanned pregnancies (Owens et al., 2017). I sought to investigate whether these differences in symptoms and outcomes were underpinned by gender-specific neural phenotypes in people with ADHD.

The neural dysconnectivity patterns associated with ADHD and studies about gender-specific functional connectivity informed my hypothesis that women and men with ADHD would show different patterns of dysconnectivity between the default mode network (DMN) and other neural networks. Like most psychopathology, ADHD is a disorder of neural systems, with symptoms arising from aberrations in functional connectivity within and between neural networks (Cortese et al., 2012; Insel, 2009). Systems affected by ADHD include the frontoparietal, dorsal and ventral attention, salience, and default mode networks involved in sustained attention and inhibitory control (Sidlauskaite et al., 2015), as well as the frontostriatal circuitry underlying cognitive control, motivation, and reward processing (Castellanos & Proal, 2012). In typically developing individuals the DMN, anchored in the medial prefrontal and posterior cingulate cortices, shows an antagonistic relationship to the task-related networks that support goal-directed behavior; the DMN is suppressed while task-relevant networks are activated to complete a task (Fox et al., 2005). In ADHD, the DMN is less deactivated (less suppressed) during goal-directed behavior (Castellanos et al., 2008; Castellanos & Aoki, 2016). As for gender-related connectivity, studies of healthy adults have found that women have more distributed, "integrated" connectivity patterns across the whole brain, and men have more localized, "segregated" brain functional organization (Zhang et al., 2016). In ADHD, there is evidence that men but not women with ADHD show brain differences relative to controls. Valera and colleagues (2010) observed that neural alterations in males were related to hyperactive symptoms, and in females with ADHD inattentive symptoms were negatively associated with functional connectivity in numerous, distributed cortical and subcortical regions (Valera et al., 2010). Taken together, these findings suggest that females with ADHD may have more variable or distributed neural phenotypes than their male counterparts, and these patterns may relate to differing behavioral outcomes and/or ADHD symptoms.

To test gender-related neural functional connectivity in ADHD, I examined associations between correlations of DMN regions with other brain networks and performance on the Rey-Osterrieth Complex Figure Test (RCFT), a measure of executive functioning that requires the participant to copy a figure containing 64 details. The RCFT taps planning, working memory, inhibitory control, attention to detail, and organization and has been shown to predict the degree of impairment due to ADHD in adulthood in females (Miller et al., 2012; Sami et al., 2003). I used resting state fMRI and a seed-based approach to test the connectivity correlations between DMN

regions (MPFC, PCC, lateral parietal, hippocampus) and the rest of the brain (Dijk et al., 2010), then I queried the resulting networks for correlations with RCFT task performance. I hypothesized that task performance would be better when DMN regions were negatively correlated with areas outside of the DMN (representing segregation from task-positive networks), and task performance would be worse when DMN regions were positively correlated with areas outside the DMN. With gender entered into the model, I hypothesized that gender-specific connectivity effects would emerge.

After 30 MRI scans I conducted preliminary data analyses and my findings made me reconsider my approach: I observed task-related connectivity associated with the DMN seeds, however, correlations between the DMN constituent regions were not apparent ($p > 0.05$, all seed-pair combinations). This was surprising given expectation that these are highly functionally and structurally connected regions. In light of this counterintuitive, null result, I did not investigate whether gender was a moderator of FC; I paused to consider why I did not observe correlations between DMN seeds. It could be that the intra-network connectivity effects in the DMN were small, requiring a larger sample size to attain significance. Or it may be that the brains I was examining were highly heterogeneous, making it difficult to find the correlations we would expect in typically developing brains. Alternatively, it could be that the analytic approach I was using was not sensitive or flexible enough to adequately assess neural network properties in this sample.

Nonetheless, across the whole sample (i.e., both genders) I did observe correlations between the DMN and task-positive regions that were associated with worse performance on the RCFT executive function task. Subnetworks of regions emerged that were correlated with the DMN seeds in the MPFC, PCC, left lateral parietal cortex, and right hippocampus. The observed subnetworks overlapped with task-positive networks including the frontoparietal network, dorsal and ventral attention networks, and a salience network consisting of the insula and cingulate cortex, networks that are particularly implicated in individuals with ADHD (Menon, 2011; Sidlauskaite et al., 2015). Co-activation of DMN regions and these task-positive networks would be consistent with a neurobiological model of ADHD, "the default mode network interference" hypothesis (Sonuga-Barke & Castellanos, 2007), which purports that weak within-DMN functional connectivity results in less cohesive DMN deactivation during goal-directed tasks and less functional segregation between DMN and task-positive networks in individuals with ADHD. The DMN interference hypothesis builds on two observations: (1) strong functional coupling between DMN nodes is found in typically developing and healthy control populations, but weaker functional coupling between DMN nodes is a common finding in children and adults with ADHD (Castellanos et al., 2008; Fair et al., 2010; Sun et al., 2012; Uddin et al., 2008); and (2) strong functional segregation between the DMN and task-positive networks is found in control populations (Fox et al., 2005), but there is decreased functional segregation between the DMN and task-positive networks in individuals with ADHD (Posner et al., 2014; for a review of the literature supporting the DMN interference hypothesis, see Castellanos & Aoki, 2016). My findings suggested that the DMN was weakly connected and incompletely suppressed in relation to goal-directed tasks in a sample of adults with ADHD. It was also apparent that specific nodes of the DMN (e.g., MPFC, PCC) may be overly connected with task-positive networks or specific nodes within task-positive networks. For example, the results suggested that the PCC was overly connected with fronto-thalamo-striatal circuits in the larger frontoparietal control network. The observed results also implicated the salience network, and the insula in particular, as abnormally

functionally connected and predictive of worse task performance. Further research is likely warranted to better understand the nature of the interactions between the DMN and sensorimotor, control, attention, and salience systems, as dysconnectivity of specific nodes of these networks may shed light on brain-behavior associations in adults with ADHD. These observations remain preliminary, as there are multiple limitations to consider.

It is difficult to study neural phenotypes in an adult ADHD population, because there is a great deal of heterogeneity associated with a life of learning and adapting with a mental illness. In addition, a core characteristic of ADHD is increased heterogeneity both behaviorally (Kofler et al., 2013) and neurally (D. a Fair et al., 2012; Mowinckel et al., 2017; Uddin et al., 2008) compared to typical development. Studying earlier time points in development during which environmental influences are minimized is a solution for addressing the changes that occur over the course of development resulting in heterogeneity (Casey et al., 2014; Insel, 2009a). Next, I may have been using suboptimal methods. Seed-based network analysis is one of many available approaches and relies on appropriate selection of *a priori* regions of interest. A data-driven approach to individual-level and group-level analyses (e.g., Sudre et al., 2017) would allow assessment of various properties of neural topological organization without constraining examination to specific seeds. This critical reappraisal of the study sample and methods, combined with an increasing appreciation for theoretical frameworks supporting the investigation of disease origins (e.g., DOHaD), culminated in a shift to studying earlier stages of development. In a personal parallel to the overview of research I reviewed at the beginning of this dissertation, work examining the effects of environmental risk factors on fetal functional neural development was well supported by my embedded experience in clinical and developmental neuroimaging, just as it has been supported in the scientific literature.

Using resting-state fMRI to investigate fetal brain functional organization, in Study 1 of this dissertation I observed an effect of maternal BMI on fetal functional connectivity such that a pair of networks—one in the left anterior insula and inferior frontal gyrus and one in bilateral prefrontal cortex—showed altered connectivity between them associated with elevated maternal BMI. These findings suggest that effects of elevated maternal BMI on fetal brain development can be seen before birth. New questions emerge, such as: What is the role of the insula in fetal neurofunctional development, and why were the effects left-lateralized? Are there genetic mediators or moderators of the effects we saw? What long-term outcomes are related to the alterations, and what is the role of the postnatal environmental? Ultimately, the answers to such questions will be illuminated by future research. The present set of studies is part of a larger, longitudinal project in which infant and child outcomes are being assessed, genetic information is being analyzed, and potential exists to investigate multiple time points of brain and behavioral functioning across development. With these data it will be possible to examine the effects of maternal obesity on neural development at multiple levels of analysis, considering behavioral and neurodevelopmental outcomes, possible genetic moderators, parenting or other psychosocial influences, and academic attainment. These future studies are not a hypothetical suggestion; they are the next step in the longitudinal research begun here.

The present findings are some of the first to populate the fetal cross-disorder connectomic "landscape" (van den Heuvel & Sporns, 2019). One other such study documented widespread connectomic disruptions in fetuses exposed to lead. Specifically, lead naïve fetuses showed

increased cross-hemisphere connectivity with advancing gestational age, but lead exposed fetuses did not (Thomason et al., 2019). In comparison, BMI-related alterations observed here were localized in the aIN/IFG and PFC; differences were focal and relatively subtle. Yet, effects located in the insula could have a big impact later in development, because this is a hub region that appears to facilitate the linking up of other networks (Ouyang et al., 2019; Song et al., 2017; Turk et al., 2019; van den Heuvel et al., 2018). BMI-related FC alterations between the insula and frontal lobe could represent vulnerability in integration circuits, which could signal diffuse and variable effects later in development. This would be consistent with the observation that maternal obesity during pregnancy is related to a wide variety of mental health and cognitive problems in offspring (Contu & Hawkes, 2017). Seemingly small or localized anomalies during the prenatal period may have large impacts downstream, but the converse may also be true: interventions during the sensitive prenatal stage may hold the greatest potential for prevention or significant reduction of later illness.

An example of an opportunity for intervention may be found in the potential link between maternal obesity and maternal-fetal attachment. Research has shown that higher MFA is associated with better physical health habits during pregnancy (Alhusen, 2012). It is possible that improving MFA would result in maternal physical health benefits that would in turn reduce obesity-related risk in the developing fetus. If this were true, an MFA intervention could support maternal and fetal health or be modularized and inserted into other treatment programs, when indicated, to tip the scale towards optimal maternal physical and mental health and resilient child outcomes. Although research in this area is scarce, there is some theorical and empirical support for MFA intervention (Akbarzadeh et al., 2016; Carter-Jessop, 1981; Olds et al., 1998; Olds & Korfmacher, 1998; Schroth, 2010). Updated measurement of MFA as described in the in-progress Study 2 (i.e., psychometrics in diverse sample, scale modernization) as well as subsequent validation of the construct will lead to clarification that will be foundational for future intervention aimed at the attachment domain.

Notably, in prenatal research the fetus is often conceptualized and represented in discourse as the subject of study, and the pregnant woman is cast as the "environment"—a separate entity/space outside of the subject, capable of influencing it and exposing it (in its dynamic and vulnerable state) to risk. Warin and Martin (2018) present cautions and suggestions regarding the history, conceptualization, and representation of the term "environment" in postgenomic science. That is, studies that investigate the short-term changes that modulate the genome, e.g., epigenetics (Warin & Martin, 2018). The authors critically discuss the DOHaD literature to caution that often "mothers are understood as environments of exposure (Landecker, 2011), reproducing long-standing discourses that blame mother for disorders in their children" (Warin & Martin, 2018; p. 710). Further, referring to the woman as "the maternal environment" can be dehumanizing. The mother-individual in prenatal research flickers in and out of personhood, in and out of being, instead, the mother-environment, synonymous with or conveying risk. Richardson (2015) also takes aim at some of the assumptions in post genomic life sciences about pregnancy, motherhood, and intervention that make the maternal body a battleground for public health interests and individual rights. A key question is: "Is there a potential for this research to heighten public health surveillance of and restrictions on pregnant women and mothers through a molecular policing of their behavior?" (Richardson, 2015, p. 211). Pregnant women in research already have flexible humanity, being more human than environment when we talk about intervention, being less human when the fetus takes center stage and the womb becomes a fixture with molecular and mechanistic

properties. There is a risk for portraying mothers as mere vehicles for intervention. It is crucial to remember that the woman is an individual making choices for herself and, to the best of her ability, her fetus. She does not (necessarily) have the expertise to parse the scientific literature, or ability to look inside her belly, or means to test beyond her fetus's developmental stage to see how the milieu of her world, her choices, and her biology will influence her future child. The in-progress Study 2 of the dissertation considers maternal attachment to the fetus, an area that has an inherently social, human view of the mother and still presents an opportunity to inform interventions for supporting families for optimally healthy pregnancies.

I also wish to highlight the relevance of these tensions between human and environment, individual and general, for people with obesity. When treating a patient whose BMI classifies them as obese, there is a tension between what is known about obesity based on research and what is known about or reported by an individual patient. The health risks associated with obesity are well known, but the fact that weight bias and obesity stigma are pervasive in health care is also well known (Foster et al., 2003; Fruh et al., 2016; Sharma & Ramos Salas, 2018). One study found that over 50% of physicians reported they view patients with obesity as "awkward, unattractive, ugly, and non-compliant" (Foster et al., 2003, p. 1168). Another study found a strong negative association between patients' weight (average, heavy, obese) and how physicians rated them on 12/13 indices, including how well the patient takes care of themselves, the seriousness of their medical problem, the level of patience the physician has for the patient, estimated patient compliance with medical recommendations, the physician's personal desire to help the patient, etc. (Hebl & Xu, 2001). It is likely that mental health providers and researchers are similarly affected by weight bias. Extended recommendations for reducing weight bias and obesity stigma are beyond the scope of the present work (although refer to Ramos Salas et al., 2017 and Sharma & Ramos Salas, 2018), but small acts like reviewing people first language are well within reason (e.g., https://odr.dc.gov/page/people-first-language). Providers and researchers alike have a responsibility to actively combat bias that systemically interferes with effective physical and mental health care and undermines respectful, equitable, high-quality research.

I have laid out the challenges confronting our field, and at the outset I provided quantitative information about public health statistics and economic disease burden to illustrate the magnitude of the problem of inadequate progress in mental health research and treatment. It is helpful to reflect briefly on some consequences of the common practice of quantifying the "burden" of mental illness. Overall, the demonstration of burden is not about merely illustrating lost human capital or money, tallying hours lived with disability or health care costs. Instead, it is about motivating people and funding organizations to recognize human suffering enough to do something about it (e.g., examine new literatures, contemplate personal values, volunteer, recommend funding to a study, incorporate new ideas or skills into clinical practice). Unfortunately, a consequence of living in a society that values quantitative information and money is that the language we use to mobilize resources emphasizes quantification and financial viability or gain. It is not actually necessary to understand or care about the realities of the disabilities that researchers and clinicians describe in order to obtain funds. Even with the best of intentions, it can be convenient to forget, if one has the privilege to do so, that we "flatten" rich lives and experiences when we quantify suffering and "pitch" the value of our work. We have a responsibility, if we are going to do this work and profit from it, to remember who we are helping and to make sure that

those individuals see some benefit. This is a goal of paramount importance, and we represent this in our grants and papers.

In what we do and what we provide to the medical and broader community, it is not obvious that we are helping. Thus, in this time of reckoning and growth within the field of psychology, I suggest that we also reflect upon how we can acknowledge and live that which we cannot yet prove, that we truly wish to improve and understand—with humility and humanity—others' experience. This acknowledgement could be something as small as thanking the participants of the study for their time in the paper; it could be keeping up with culturally humble recommendations for discussing marginalized groups (French et al., 2020); or it could be donating excess profits back to research or volunteer organizations that directly benefit individuals with mental illness. The stage for this reflection is set, also, by this time of national reckoning in the United States regarding our country's history of and current racism. Ours is a time that is characterized by global pandemic and national protests related to the Black Lives Matter movement following the killing of George Floyd by police officers in Minneapolis, MN (Hill et al., 2020; Hutchens, 2020; Luscombe & Ho, 2020) and Breonna Taylor in Louisville, KY. It is a time of increased suffering and increased recognition of suffering. The concreteness of our humanity has never been more important; the need for concrete actions from our work as mental health researchers and providers has never been more urgent.

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Table 1. Data Summary: Participant Characteristics and BMI Spearman Correlations

Prenatal Variables	**Mean**	**SD**
Fetal gestational age at MRI (weeks)	33.5	3.7
Maternal age at MRI (years)	25.2	4.4
Maternal BMI	33.2	6.3
Maternal Physical Health		
Total (Composite)	191.2	27.1
Diet	63.2	13.3
Exercise	28.8	7.1
Medical Adherence	28.1	5.2
Substance Abuse	49.2	5.8
Sleep	22.6	5.6
Maternal Mental Health		
STAI Total	35.8	8.3
CES-D Total	13.5	8.6
Maternal Ethnicity, ***n (%)***		
African American	*92*	*8%*
Caucasion	*9*	*84%*
Multiracial	*4*	*4%*
Not Reported	*4*	*4%*
Maternal Education, ***n (%)***		
No GED/Diploma	*18*	*17%*
GED/Diploma	*42*	*39%*
Some College	*39*	*36%*
2 Year Degree	*1*	*1%*
4 Year Degree	*3*	*3%*
Graduate Degree	*2*	*2%*
Not Reported	*4*	*4%*
fMRI Data Characteristics		
# fMRI frames analyzed	158.2	42.9
Translational movement (mm)	0.2	0.1
Rotational movement (degrees)	0.4	0.2
Birth Outcomes		
Fetal gestational age at birth (weeks)	39.0	1.5
Birth weight (g)	3208.0	517.6
Correlations with BMI (Spearman)	***r***	***p****
Fetal gestational age at MRI (weeks)	-0.13	0.18
Health Total (Composite)	0.1	0.3
Diet	0.13	0.2
Exercise	0.04	0.68
Medical Adherence	0.1	0.32
Substance Abuse	0.09	0.38
Sleep	0.07	0.48
STAI Total	0.08	0.43
CES-D Total	-0.04	0.72
Translational movement (mm)	0.05	0.6
Rotational movement (degrees)	0.08	0.39
Correlations with BMI adjusted for pregnancy (Spearman)		
Fetal gestational age at MRI (weeks)	-0.08	0.42

**uncorrected*

Table 1. Summary of maternal and fetal participant characteristics, correlations between BMI and potential confound variables.
Maternal physical and mental health were measured using self-report rating scales. The adapted Health Practices Scale consists of 53 items on which participants rank from 1=never to 6=always the frequency of engaging in health behaviors (e.g., "Have blood pressure checked regularly"). The State-Trait Anxiety Inventory (STAI) consists of two 20-items subscales measuring current and longstanding anxiety. Per subscale, scores indicate "no or low anxiety" (20-37), "moderate anxiety" (37-44), and "high anxiety" (45-80). The Center for Epidemiological Studies-Depression scale (CES-D) consists of 20 items on which participants rank their experience of depression symptoms during the past week. Scores above 16 indicate clinically significant depression symptoms.

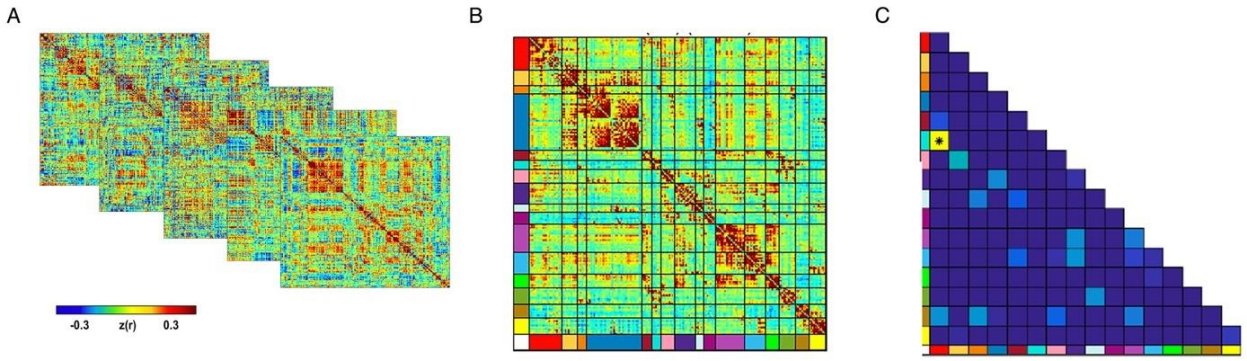

Figure 1. Overview of fetal fMRI statistical approach. Pearson correlation matrices (panel A) reflecting 197 ROIs for each participant were analyzed to create a subnetwork model of the fetal brain. The complete set of unique n=19,306 ROI-pair functional connectivity (Fisher-z) values from all participants were then averaged, producing a 197x197 connectivity matrix (panel B). In order to test the effects of maternal BMI at the network-pair-level, enrichment analysis was then performed to identify individual ROI pairs with functional connectivity related to maternal prenatal BMI, and, subsequently Chi-squared statistic was used to determine whether the number of significant ROI-pairs ($p < 0.05$) within a network-pair was greater than expected by chance (panel C). This approach was developed by Eggebrecht and colleagues (Eggebrecht et al., 2017).

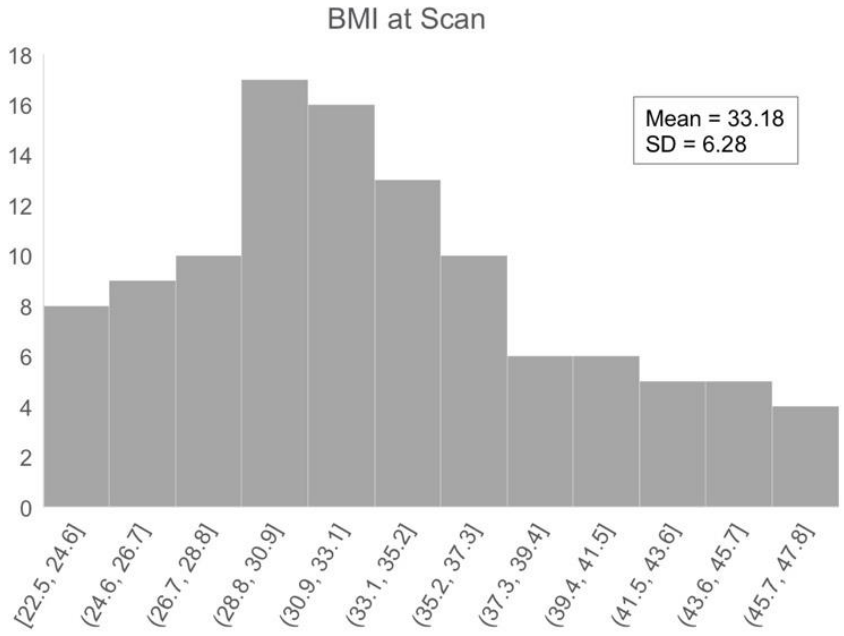

Figure 2. Distribution of maternal BMI at the time of MRI assessment. Participants (N = 109) varied in length of pregnancy from 26 to 39 weeks.

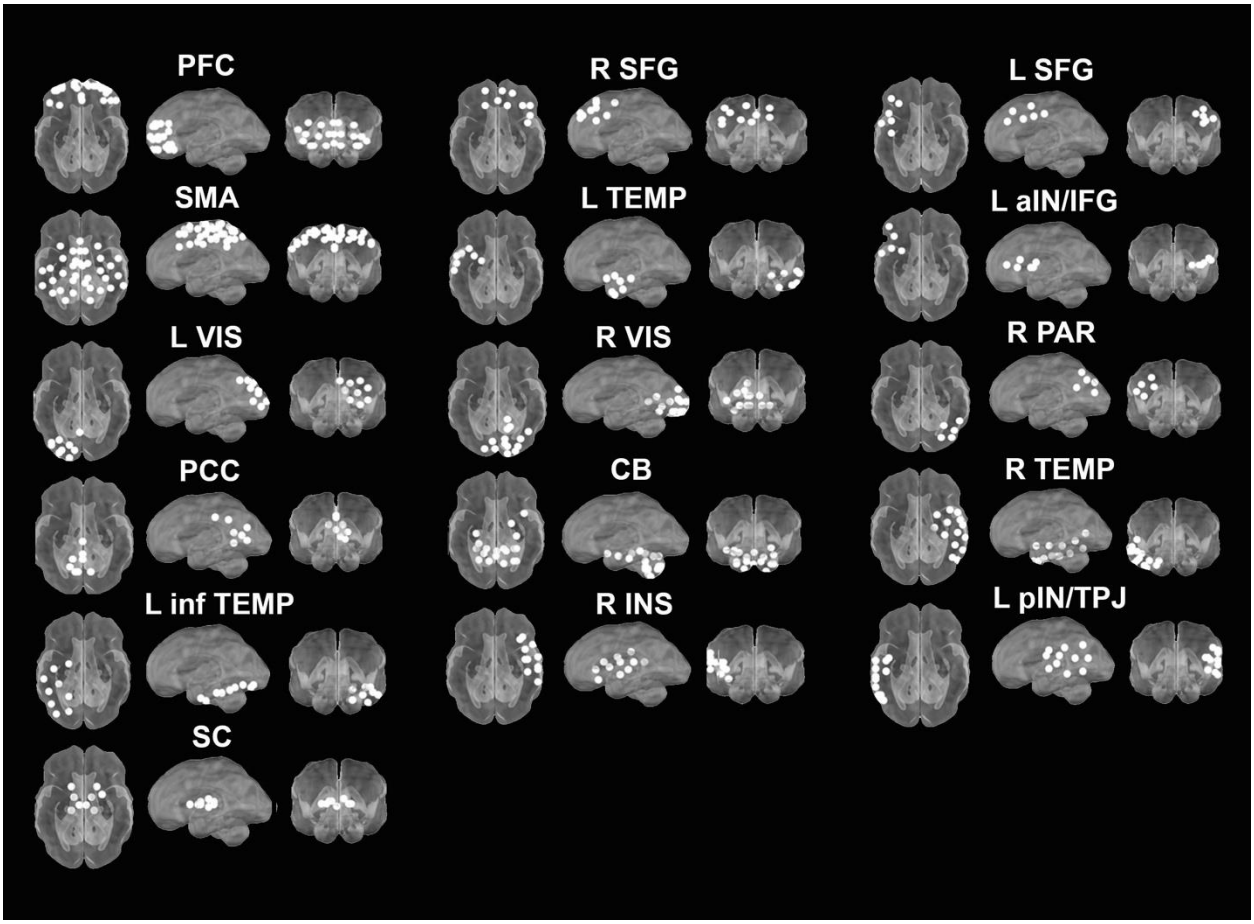

Figure 3. Automated consensus procedure for identifying fetal brain subnetworks. Infomap community detection algorithm was used to assign ROIs to neural subnetworks based on maximization of within-module random walks applied to adjacency matrices at each threshold. Solutions for each threshold were combined using an automated consensus procedure to provide a single model of the community structure by maximizing the normalized mutual information of groups of neighboring solutions and then maximizing modularity. This network solution resulted in an optimal solution of 16 fetal brain subnetworks encompassing fetal cortex, subcortical structures, and the cerebellum.

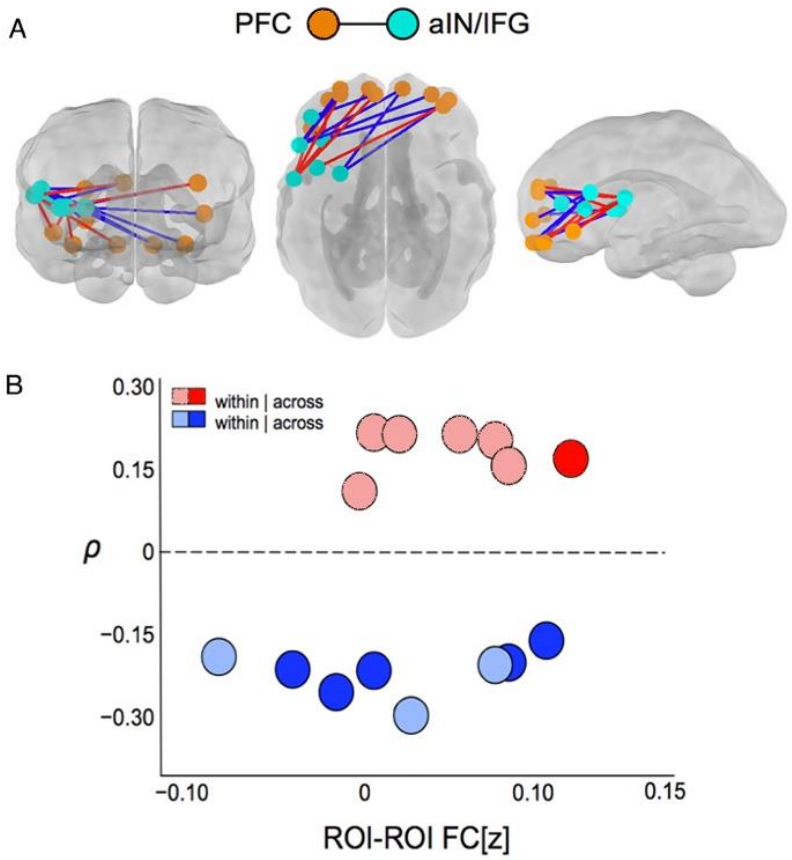

Figure 4. Maternal BMI was associated with variation in fetal brain functional connectivity (FC) across subnetworks that encompass bilateral anterior prefrontal cortical regions (orange spheres) and left anterior insula/inferior frontal gyrus (teal spheres; panel A). Both positive (red lines) and negative (blue lines) BMI-FC correlations were observed, indicating that increasing BMI related to both increases and decreases in FC. Strength of significant BMI-FC correlations (FC[z]) ranged from -0.80 to 1.06. Increased FC associated with increasing BMI tended to connect regions unilaterally within the left hemisphere, whereas decreased FC was more often observed in cross-hemispheric connections.