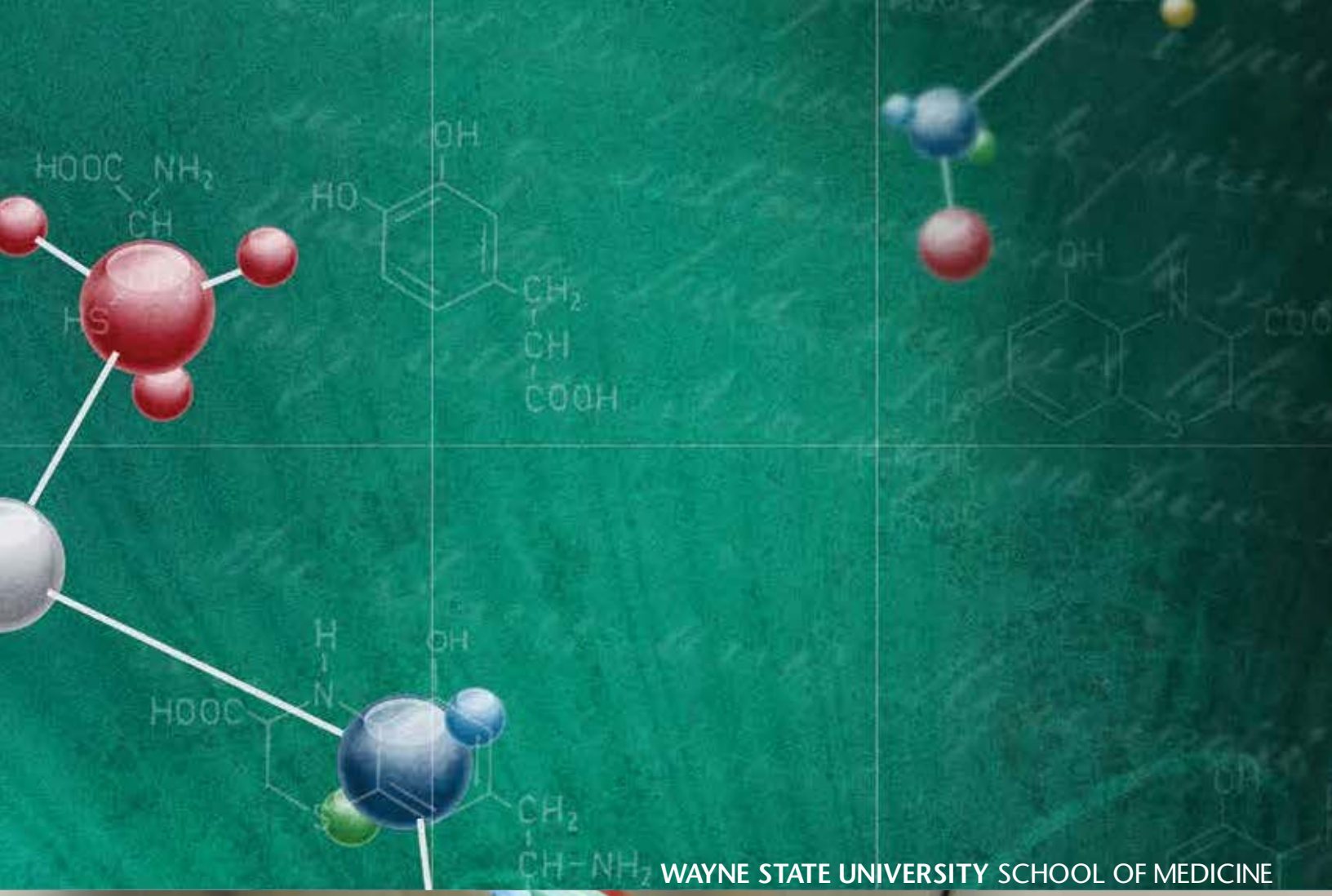

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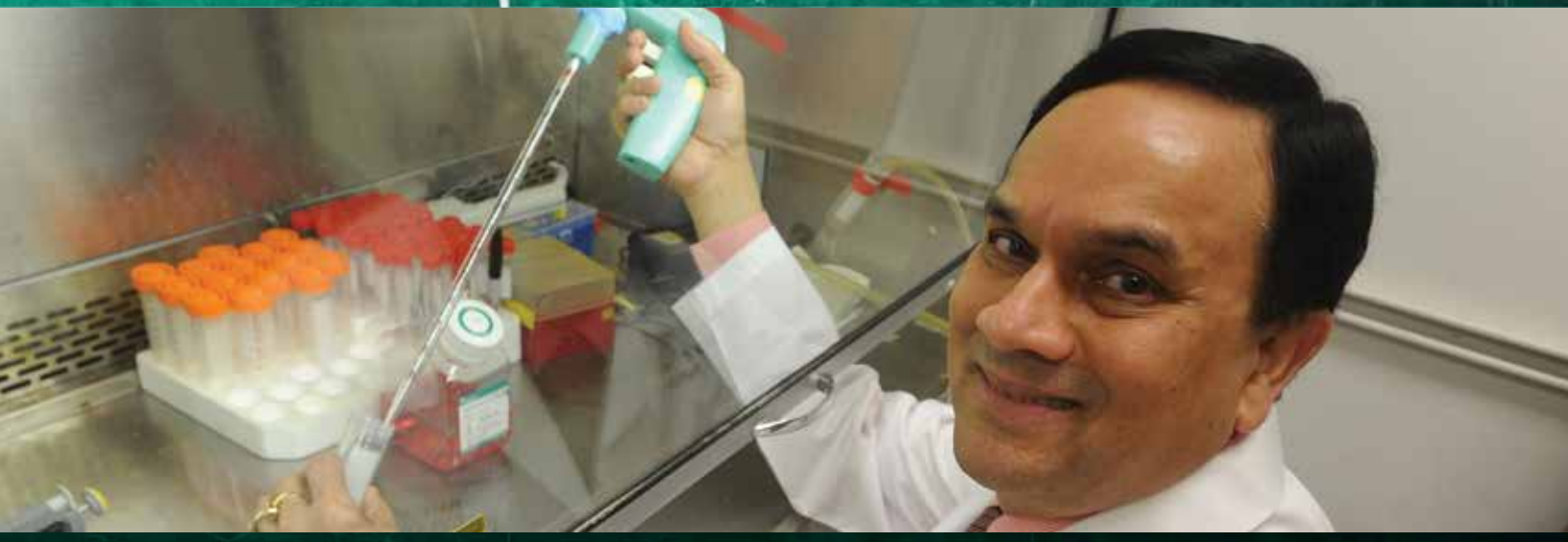

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Beyond gray matter

Investigators exploring link between brain function *in utero* and developmental outcomes later in life

by **Andrea Westfall**
photos by **Rob Widdis**

Tracey Moses was four months pregnant when genetic testing revealed her baby could be born with a severe disability or deformation and might not live past his first birthday.

The Detroiter was older than 40, and up to that point, disappointed with the quality of her prenatal care. She also was determined to enjoy her third pregnancy — her first since giving birth to a son 19 years earlier. "It had been 20 years since I had a child, and I wanted the best care," she said.

Fear of the unknown lingered. She learned about an open-ended, multi-part baby development study being conducted by Wayne State University researchers while attending an appointment at the Center for Advanced Obstetrical Care and Research in the Detroit Medical Center's Hutzel Women's Hospital, part of the National Institutes of Health's Perinatology Research Branch at the WSU School of Medicine. She enrolled in the study, where she would be considered a "typical" pregnancy, serving as a normal community sample but on the "high-risk" end of the healthy spectrum.

"I knew, being involved in the study, no stone would be left unturned. I know I'll be getting the best care for my baby, so that's why I participated; the one-on-one attention," she said. "I couldn't have had such a relaxed pregnancy unless I was in the study."

A multi-disciplinary team of faculty, fellows and graduate student researchers from the School of Medicine, the Merrill Palmer Skillman Institute for Child and Family Development, and the Psychology Department teamed up in 2011 to launch what they dubbed the PINC/PURPLE project — a WSU-funded study officially known as "Perinatal Imaging of Neural Connectivity/ Parent Representations during pre- and postnatal Periods Linked to Early Outcomes."

The PINC portion of the study focuses on recording spontaneous activity in the fetal brain, while the mother is still pregnant, using resting-state functional magnetic resonance imaging. This pioneering work, which began at the School of Medicine's MRI Research Facility in November 2011, will map functional connections in the developing fetal brain.

PINC is directed by neuroscientist Moriah Thomason, Ph.D., an assistant professor of Pediatrics in the School of Medicine and in MPSI. She is also director of the Unit on Perinatal Neural Connectivity at the Perinatology Research Branch and affiliate faculty in the Department of Psychology. She estimates there are fewer than 10 published reports that have used fMRI to study the human fetal brain, and none that have quantified fetal brain functional connections using resting-state MRI.

"Our studies will offer insight into how brain networks become formed in utero, and will also be applied to study the effects of premature birth and pregnancy-related health complications on fetal brain development," Dr. Thomason said.

Before joining the WSU faculty in March 2011, Dr. Thomason spent 12 years at Stanford University School of Medicine, using MRI in children and adolescents for similar purposes. She collected pilot data for the PINC study at Stanford, using adult images to prepare for potential movement corrections needed after processing. But when it came time to look at

The WSU professors leading an open-ended, multi-part baby development study are, from left, infant mental health expert **Ann Stacks, Ph.D.**; neuroscientist **Moriah Thomason, Ph.D.**; and developmental psychologist **Marjorie Beeghly, Ph.D.**, pictured in the courtyard of WSU's Merrill Palmer Skillman Institute.

Dr. Moriah Thomason's study focuses on recording spontaneous activity in the fetal brain, while the mother is still pregnant, using resting-state functional magnetic resonance imaging. This pioneering work, which began at the School of Medicine's MRI Research Facility in November 2011, will map functional connections in the developing fetal brain. Images of a baby at 25 weeks gestational age are pictured behind her.

developing fetal brains, her former employer lacked the components she needed, including a diverse population with a high rate of premature births.

In 2008, more than 17 percent of births in Detroit were preterm, nearly 5 percent higher than the national average, according to one of the latest reports from the Michigan Chapter of the March of Dimes.

"We couldn't do this anywhere else," Dr. Thomason said.

To gauge brain development, the study enrolls a mix of mothers at high risk for premature birth and those expected to carry their babies to full term. "The event of being born premature has an effect on the brain development of these young infants, but we do not know if those effects result from events occurring during the pregnancy, or, alternatively, if the brain is particularly vulnerable to injury as a result of life outside of mother beginning too soon," she said.

The field of obstetrics doesn't have accepted evidence that the brain is developing differently in fetuses that will be born preterm. By using MRI advances, though, "one objective is to map what has not been mapped, to study neural connectivity in the premature brain because it may offer insight into the genesis of developmental disorders that are commonly attributed to early delivery," she added.

For PINC, Dr. Thomason images a variety of pregnant women at different gestational stages to assess fetal structural and functional brain development. Her collaborators and team also assess the mothers' prenatal psychosocial adaptation and stress reactivity, and explores women's mental representations of their fetuses. The fMRI is safe for mother and baby, and the procedure takes only about 45 minutes. During the visit, she also takes salivary cortisol samples to record the mother's stress levels — insight into what the biological environment of the mother is like during pregnancy.

Her goal is to bring brain scans in utero — and WSU's role in that pursuit — to the forefront of what neuroscientists across the world are trying to determine: Even before birth, could the brain broadcast clues to how a child might develop socially and emotionally?

The PURPLE portion of the study is co-directed by Ann Stacks, Ph.D., assistant professor of Research at MPSI and director of the Infant Mental Health Program; and Marjorie Beeghly, Ph.D., associate professor of Psychology and affiliate faculty at MPSI. The importance of parenting and parent-child relationships in shaping children's developmental outcomes is a primary research interest for both.

"Together, we, and the staff on the PINC and PURPLE teams, expect our combined study will shed important new light on the specific prenatal and postnatal bio-psychosocial factors that are most predictive of children's positive developmental and behavioral outcomes in both typical and at-risk groups," Dr. Beeghly said.

"I believe this is truly pioneering work, as no one knows yet what 'normal' fetal brain development looks like at different gestational ages during pregnancy," said Dr. Beeghly, a developmental psychologist with nearly 20 years of experience conducting longitudinal child development and parenting studies in

at-risk, delayed and typical populations of infants and parents. "We don't know, for instance, to what extent typical fetal brains show variation in the timing of when different regions get connected, the extent of the connectivity, denser versus sparser connections, and so on. We also don't know the meaning of such individual differences with respect to infants' later developmental or behavioral outcomes."

"This is especially the case for infants at risk for preterm birth," Dr. Thomason said. "Something may be going on in the uterine environment that alters the way the brain connections are formed." Because of that environmental factor, the fMRI is just the first step in a series of follow-ups that Dr. Thomason believes could help science achieve a clearer understanding of how early brain functional development during pregnancy affects childhood development. And that's where PURPLE comes into play.

The first postnatal assessment infants receive is the Brazelton Neonatal Behavioral Assessment Scale, administered during the infant's first week of life by Dr. Beeghly and PURPLE team staff.

Established research proves the brain is shaped by environment, with important implications for children's later outcomes, especially social emotional functioning. The PURPLE team also places a strong emphasis on postnatal environmental measures in its assessment.

"If you want to predict children's outcomes accurately, you need to consider environmental factors such as maternal well-being and the quality of the child's proximal caregiving environment," Dr. Beeghly said. "Quality of caregiving appears to be especially influential for the outcomes of biologically at-risk children."

In other words, parenting is just as important as the way a baby is pre-wired, and even more so when pre-birth brain scans show a possible developmental delay or behavioral issue could manifest down the road.

"Social interactions with caregivers shape and change their brains," Dr. Stacks added. For example, infants who are maltreated respond differently to stressful situations than infants living in warm, nurturing households, she said. Babies living in what's considered an unsafe environment with a parent classified as "harsh" or "insensitive" develop differently than those with a sensitive parent.

Moriah Thomason, Ph.D., WSU assistant professor of Pediatrics, checks in with 6-month-old Ella and her mother, Rebecca Dorn-Wheeler, before the Still-Face paradigm is administered by Marjorie Beeghly, Ph.D., associate professor of Psychology. Dorn-Wheeler is a WSU doctoral student who also works on the PINC/PURPLE study.

Aside from analyzing a baby's development, Dr. Thomason wants to use the fetal brain data collected in PINC to map, as early as possible, the order, timing and patterning of brain functional development. This effort aligns with the National Institutes of Health's Human Connectome Project — a $40 million initiative to map the neural pathways that underlie all human brain function, launched in 2010.

Dr. Thomason believes she will prove that a default mode network — a "very critical and essential foundational network" — exists in fetuses earlier than previously thought. The default mode network is a network of brain regions that are active when an individual is awake but resting. According to the Society for Neuroscience, it is thought to be responsible for internal tasks such as daydreaming, retrieving memories, thinking about the future and gauging others' perspectives, and according to several published reports, may be relevant to Alzheimer's disease, schizophrenia and autism.

Assistant Professor of Pediatrics **Moriah Thomason, Ph.D.**, reviews with WSU students **Amy Anderson**, right, and **Maya Dassanayake**, left, images of a fetus taken with magnetic resonance imaging while the mother was 25 weeks pregnant.

The presence of a pre-birth default mode network suggests its existence is foundational to the development of other networks. This conclusion is unanticipated, as the default mode network is most often conceptualized as a cognitive network, and more primitive networks would be expected to emerge earliest in development. "Increasingly, research is indicating it's really the early life events that foretell later outcomes," Dr. Thomason said. "There is nothing sooner than this (in utero) period."

For children at risk for poor developmental outcomes, the brain can still be shaped by a nurturing environment, which includes sensitive parenting, Dr. Stacks said. Her research focuses on the impact that the caregiving environment has on children's social and emotional development, specifically their attachment representations and behavior at home and school. She poses the question, "What happens if you take two infants whose development is known to be at-risk but they are raised in homes with two different parenting styles?" It is likely that their attachment representation will be different, which can either protect them from risk or become an additional risk factor. Humans are hard-wired to form an attachment. But the form of attachment — secure, insecure or disorganized — is key. Children with a secure attachment tend to be more socially competent, whereas children with a disorganized attachment are at higher risk for emotional and behavioral disorders. Children with disorganized attachment at 12 months old are more likely to exhibit severe behavioral problems at age 2. These behavior problems can persist into adulthood.

When infants are 4 and 9 months old, the PINC staff calls mothers to complete a brief developmental screening over the phone to find out whether infants are showing developmental delays relative to published

norms. At 7 months old, mother and infant come to the play lab at WSU for a formal evaluation of the child's developmental skills, mother-infant social interaction and maternal interviews by the PURPLE team. The infants' cognitive, language and motor skills are evaluated using the Bayley Scales of Infant Development III, a widely used age-referenced developmental assessment. Then, individual differences in parent-infant interactive behavior and stress reaction are evaluated during the Still-Face paradigm, a videotaped observation during which the mother interrupts her normal behavior with the baby by briefly holding a non-responsive "still-face" while continuing to look at the baby. Dr. Beeghly said behavioral and physiological reactions during the Still-Face paradigm suggest that infants find their mother's still-face stressful, perhaps because it violates the child's expectation based on usual behavior or breaks the rules of what is supposed to happen during typical infant-mother interactions. Like Dr. Thomason, the PURPLE team also collects salivary cortisol samples from the mother and infant before and after the Still-Face paradigm to measure variations in maternal and infant physiological reactivity to this social stressor. The maternal cortisol measures will be combined with the cortisol measures collected by the PINC team during pregnancy to evaluate stability and change in maternal stress over time.

At 15 months old, infant and mother visit the play lab again, this time to evaluate parent-infant attachment, reassess maternal and infant stress levels, and check that developmental milestones are being reached.

"The eventual product of our work will be data that can be used to make predictions about sound courses for treatment. People wonder about prenatal stress and how that affects the brain," Dr. Stacks said. "Is there something we can do prenatally to help put kids on the right course?"

Dr. Beeghly asked, "Can positive parenting attenuate the possible harmful effects of compromised fetal brain development and/or high-risk birth on children's outcomes? The rich longitudinal data we are collecting in the PINC/PURPLE study have the potential to address these questions."

As for Tracey Moses, she decided she would put her faith in God, but with a caveat: "There's nothing wrong with having a little insight with technology," she said.

The MRI revealed all was developing normally. "I was really pleased, because when the results came back it was everything I expected. I thought it was a blessing. I thought, 'Now I know we can get down to business,'" she said.

Rebrick Copeland Jr. was born Dec. 14, 2011. He is meeting all of his expected developmental milestones, sometimes earlier than normal. "He's doing fine," she said. "I think he's going to be our little brainiac. Our genes are going to do well." ■