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Research Shows Early Brain Changes Precede Neurological Disorders

Studies reveal altered brain networks in very young subjects

CHICAGO — Research released today provides new insights about the earliest brain changes associated with a variety of neurological disorders, including autism spectrum disorder and disabilities following pre-term birth. The studies reveal abnormalities in brain circuitry that are established even before symptoms arise. The findings were presented at Neuroscience 2015, the annual meeting of the Society for Neuroscience and the world's largest source of emerging news about brain science and health.

Some of the neurological diseases and disorders that are most challenging to understand are those that trace back to infancy or the period before birth, the most critical times in human development. Connections between brain regions that form *in utero* are emerging as important determinants of later brain function.

Today's new findings show that:

- Cortisol level in mothers' milk is linked to social and cognitive development in monkeys (Amanda Dettmer, abstract 468.08, see attached summary).
- Structural and functional connectivity between brain areas is weaker in babies born prematurely (Cynthia Rogers, abstract 349.08, see attached summary).
- Motor impairments linked to preterm birth may stem from brain connectivity abnormalities present before birth (Moriah Thomason, abstract 252.01, see attached summary).
- Some cases of autism spectrum disorder (ASD) have been linked to an antibody found in the maternal bloodstream. Injecting the antibody into pregnant mice leads to brain abnormalities and ASD-like symptoms in male offspring (Lior Brimberg, abstract 655.01, see attached summary).
- Children who will develop Huntington's disease as adults show weak connections between disease-related brain areas (Jessica Lee, abstract 42.03, see attached summary).

"These studies illustrate how the brain's structural and functional architecture is exquisitely sensitive to conditions before birth and how alterations to brain circuitry can set the scene for future neurologic impairment long before it arises," said Jay Giedd, MD, University of California, San Diego, an expert on the developing brain. "These new discoveries could one day help lessen the burden of early-life neurologic abnormalities."

This research was supported by national funding agencies such as the National Institutes of Health, as well as private and philanthropic organizations. Find out more about brain development and neurological disorders at *BrainFacts.org*.

Related Neuroscience 2015 Presentation:
Special Lecture: Nature and Nuture in Synapse Development, Maturation, and Disease
Sunday, Oct. 18, 2:30-3:40 p.m., Hall B1

Abstract 468.08 Summary

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Hormone in Mother's Milk May Influence Social, Cognitive Development

*Elevated cortisol content associated with less impulsivity in baby monk*eys

Mothers' milk is appreciated for the nutritional and immunological benefits it bestows on infants, but new research in monkeys shows that its hormonal content may influence cognitive and social development. The findings were released today at Neuroscience 2015, the annual meeting of the Society for Neuroscience and the world's largest source of emerging news about brain science and health.

Researchers studied 26 rhesus monkeys and their infants for the first eight months of life — equivalent to about age two and a half in humans. During the first month after birth, the investigators collected samples of the mothers' milk and measured the level of cortisol, best known as the stress hormone. Previous studies have linked high cortisol levels in milk to a more nervous temperament in humans and monkeys, but social and cognitive aspects of development had not been investigated.

In a task involving reaching for marshmallows designed to test impulsivity, baby monkeys who had milk with higher levels of cortisol in the first month of life displayed less impulsive behavior at age six months. Additionally, "higher cortisol in mother's milk was associated with less initiation of social behaviors like grooming and play — but only for male infants," said lead author Amanda Dettmer, PhD, of the National Institute of Child Health and Human Development at NIH.

Dettmer said this research supports the "lactational programming" hypothesis that breastfeeding affects neurological growth, and it "supplements previous studies in human and nonhuman primates showing that hormones in mother's milk play a significant role in infant neurological and behavioral development." Further research on mothers' milk could reveal early biological mechanisms involved in brain development and lead to the development of better artificial milk sources such as formula.

The research was supported with funds from the National Institutes of Health, including the Division of Intramural Research at the Eunice Kennedy Shriver National Institute of Child Health and Human Development.

Scientific Presentation: Tuesday, Oct. 20, 8-10 a.m., S405

468.08, Cortisol in mother's milk in the neonatal period predicts later cognitive performance and social behavior in infant rhesus monkeys (Macaca mulatta)
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TECHNICAL ABSTRACT: Mother's milk is known to contain constituents that are crucial to infant development, yet the role of hormones in early mother's milk on later infant cognitive and social behavior remains unexplored. Recent research has focused on "lactational programming," whereby hormones in milk, namely cortisol, act to program infant growth and temperament. We studied N=26 rhesus monkey (Macaca mulatta) mother-infant dyads born and reared in large social groups from birth through weaning at 8 months. We sought to determine the role of cortisol in mother's milk in the neonatal period on cognitive performance on an inhibition task, and on social behavior with peers later in development. We collected milk twice in the first 30 postnatal days and analyzed the samples for cortisol content. Beginning at 6 months of age, a subset of infants (n=8) was given a cognitive task five days per week to assess impulsivity/response inhibition. From 4-8 months of age, a larger subset of infants (n=24) was observed twice weekly for 10mins each to record the occurrence of social behaviors (i.e., play, grooming, mounting), both initiated and received. Regression analysis revealed that average cortisol in mother's milk in the first 30 days of life negatively predicted "balk" rates (i.e., % trials the infant refused to participate; $R2=0.43$, $p=0.045$) and "bonk" rates (i.e., % trials the infant responded with an impulsive response; $R2=0.67$, $p=0.026$) on the cognitive task. Moreover, average milk cortisol also negatively predicted the frequency of initiated social behaviors, but for males only ($R2=0.37$, $p=0.043$). These findings support the "lactational programming" hypothesis and supplement previous findings in humans and monkey infants that cortisol in mother's milk predicts negative affect/cautious temperament (Grey et al., 2013; Hinde et al., 2014). Collectively, our results point to a role for hormones in mother's milk, beginning at birth, in subsequent infant neurological and behavioral development. Future studies will be able to draw upon these results to determine the mechanisms for this type of programming.

Abstract 349.08 Summary

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Preterm Birth May Weaken Functional and Structural Brain Connectivity

Network changes may underlie heightened risk for psychiatric disorders

Prematurely born infants are at increased risk of developing neurological and psychiatric disorders, and new findings released today suggest that this increased risk may be linked to early changes in the brain's structural and functional connections. The research was presented at Neuroscience 2015, the annual meeting of the Society for Neuroscience and the world's largest source of emerging news about brain science and health.

One of every nine infants in the U.S. is born early, making it more likely that they will develop disorders such as autism spectrum disorder (ASD), attention deficit and hyperactivity disorder (ADHD), and anxiety disorders. To get a better picture of the developmental consequences of preterm birth, the researchers used multiple types of brain imaging to compare the brains of 58 babies born at full term with those of 76 infants born at least 10 weeks prematurely. They used functional magnetic resonance imaging (fMRI) and diffusion tensor imaging (DTI), a technique that measures water movement in the brain and reflects structural connectivity between brain areas, to measure structural and functional connections between regions that make up seven key brain networks.

White matter tracts — made of axons that connect brain regions to one another and form brain networks — were significantly altered in the brains of preterm babies compared with full-term babies. Functional connections were also compromised in the preterm children. The greatest differences between term and preterm babies were seen in connectivity in the default mode network (DMN) and the frontoparietal network, brain circuits associated with attention and emotion that have been linked to disorders such as ADHD and ASD.

"Brain networks related to attention, communication, and affective processing all had decreased strength in the brains of the premature infants," said lead author Cynthia Rogers, MD, of Washington University in Saint Louis. "We believe these findings may help explain why children born prematurely have such an elevated risk of psychiatric disorders."

This research was supported with funds from the National Institute of Mental Health, the National Institute of Neurological Disorders and Stroke, the National Institute of Child Health and Human Development, the McDonnell Center for Systems Neuroscience, the Child Neurology Foundation, the Cerebral Palsy International Research Foundation, and the Dana Foundation.

Scientific Presentation: Monday, Oct. 19, 10-11 a.m., Hall A

349.08, Impact of preterm birth on structural and functional connectivity in neonates
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TECHNICAL ABSTRACT: Premature birth is a deleterious early life stressor associated with altered cerebral gray matter and white matter development. It is also associated with developmental deficits and increased rates of psychopathology including ADHD, Autism Spectrum Disorder and anxiety disorders. There is increasing evidence these developmental deficits may be subsequent to altered cerebral development, particularly in those children born at the earliest gestational ages. However, few studies have applied multimodal imaging techniques to concomitantly assess structural and functional connectivity in this population. This study compared structural and functional connectivity in very preterm infants (VPT; gestational age<30 weeks; N=76) without significant brain injury to that of healthy, full term infants (FT; gestational age>37 weeks; N=58). All infants underwent MRI at term-equivalent age (36-42 weeks postmenstrual age), including acquisition of diffusion tensor imaging (DTI) and resting state fMRI (rs-fMRI) sequences. DTI data was analyzed using tract based spatial statistics (TBSS), assessing group differences in fractional anisotropy (FA). rs-fMRI data was analyzed to determine measures of correlation and covariance within and between seven canonical resting state networks (RSNs). TBSS results demonstrated widespread reductions in white matter tract FA in VPT versus FT infants (Figure 1A). VPT infants also demonstrated reduced correlation and covariance within and between all RSNs (Figure 1B). Among RSNs involved in attentional, social-communicative and affective processing, the default mode (DMN; p=.001) and frontoparietal (FPC; p<.001) networks were notably affected. White matter tracts connecting hubs of these RSNs (e.g., cingulum, anterior limb internal capsule) were among those demonstrating greater between group differences. These results suggest preterm birth causes widespread disruption of functional and structural connectivity of the developing brain, including regions linked to the psychiatric disorders that occur commonly in preterm children.

Abstract 252.01 Summary

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Tracing the Roots of Motor Impairments in Preterm Babies

Alterations in brain connectivity are present before birth

New research indicates that altered brain connectivity is present before birth in prematurely born babies, suggesting that their brains are prewired to develop a range of motor impairments often seen in children born preterm. The research was presented today at Neuroscience 2015, the annual meeting of the Society for Neuroscience and the world's largest source of emerging news about brain science and health.

The researchers pioneered new technology that allowed them to use functional magnetic resonance imaging (fMRI) to scan the brains of fetuses still inside the womb. They recruited pregnant women for the study, some of whom were at high risk for preterm delivery. All fetuses (and their mothers) were scanned around gestational week 30. Eighteen of the fetuses went on to be born prematurely, while 18 others were born after gestational week 37, considered to be full term.

"We observed that activity in the motor system of the brain was more coordinated in fetuses that went on to be born at term, suggesting that this system was already more developed in term-born fetuses," said lead author Moriah Thomason, PhD, of Wayne State University in Detroit. "We also found that differences between the two groups were greatest in connections that were physically far apart. Thus, while local connections appear relatively preserved in preterm fetuses, the preterm brain may have delayed development of distant connections." That failure to connect far-away brain regions *in utero* may underlie the motor deficits seen later in preterm babies.

"Identifying alterations in neural networks before birth will provide a greater understanding of preterm brain development, leading to new ways to prevent and treat irregular neural connections that, in many infants, accompany prematurity," Thomason said.

This research was supported with funds from the Perinatology Research Branch of the National Institute of Child Health and Human Development, and the National Institute of Environmental Health Sciences.

Scientific Presentation: Sunday, Oct. 18, 1-2 p.m., Hall A

252.01, Neuroconnectivity in human fetuses subsequently born preterm
***M. E. THOMASON**[1,4], D. SCHEINOST[5], J. H. MANNING[2], L. E. GROVE[2], P. K. JELLA[3], K. M. HERMEZ[2], J. L. HECT[2], S. JIRJIS[2], R. T. CONSTABLE[5], L. R. MENT[5], R. ROMERO[4];
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TECHNICAL ABSTRACT: Many infants born preterm demonstrate mild to severe motor abnormalities. It is difficult to ascertain whether motor impairments result from altered neurological development in utero, as opposed to secondary injury. Functional connectivity mapping via resting state fMRI can measure fetal brain function before birth. It is thus possible to identify alterations in neural networks that present before birth to ascertain origins of neurological anomaly associated with preterm birth. We tested the hypothesis that altered motor network development precedes preterm birth. We enrolled pregnant women, some of whom were high-risk for preterm delivery, but who were experiencing otherwise healthy pregnancies. We compared 18 fetuses born prior to 37 weeks to 18 term-delivered fetuses matched on age, gender and motion during MRI. Postmenstrual gestational age (GA) at the time of the scan and sex of fetuses subsequently born preterm (PT) were 29+5 (weeks+days; SD=3+4), 11 males; age and sex of term-born control fetuses (TC) were 30+1 (SD=3+3), 10 males; study sample range was 22-36 weeks GA. We measured brain function in utero using non-invasive resting-state functional MRI. Functional data were co-registered to a 32-week gestational age fetal template. Seed-based connectivity analyses were used to compute signal covariance maps from 5 regions in the left motor cortex and cerebellum, and in one control region. All analyses were conducted at uncorrected $p \leq 0.001$ and $k \geq 10$. We observed increased functional connectivity in TC compared to PT fetuses from motor and cerebellar seeds. Between group differences were greatest in distant brain regions, suggesting that PT fetuses lack long-range connectivity. In contrast, increased short-range connectivity was observed in PT fetuses, providing some evidence for a trade-off in local over distal connectivity in the PT fetus. Differences between groups were smaller in the parietal network that served as a control, indicating specificity in these observations. Here, we shift the timeline for discoveries about functional brain maturation to a time of exceedingly rapid change, the fetal period, when foundations for brain circuitry are being laid. For the first time we report altered neural connectivity in fetuses that will be born preterm. Reduced long-range and cross-hemispheric connectivity in PT fetuses indicates that deficient neuroconnectivity in the prenatal period precedes disturbances in motor learning in infancy. Scientific data that can non-invasively operationalize functioning of the fetal brain has the potential to transform our understanding of this sensitive and defining period in human life.

Abstract 655.01 Summary

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Maternal Antibodies: Risk Factors for Autism Spectrum Disorder

Brain-reactive immune proteins lead to altered brain structure, behaviors in male mice

Some cases of autism spectrum disorder (ASD) have been traced to antibodies found in the mother's bloodstream that may affect the vulnerable fetal brain. A new study shows that one such antibody isolated from a mother of an ASD child caused structural brain changes and ASD-like behaviors in male mice, suggesting that a subset of cases of autism spectrum disorder might be preventable by blocking maternal antibodies. The findings were released today at Neuroscience 2015, the annual meeting of the Society for Neuroscience and the world's largest source of emerging news about brain science and health.

Autism spectrum disorder refers to a group of complex brain development disorders characterized by difficulties in social interaction and communication, repetitive behaviors, and motor dysfunction. In the U.S., ASD is estimated to affect 1 in 68 children. The causes of ASD remain unknown, but brain changes start very early in life, most likely *in utero*. Researchers have previously identified genetic variants that may contribute to ASD, but ASD can likely also be caused by environmental risk factors, perhaps found in the *in utero* milieu. Factors that may harm the fetal brain include maternal antibodies — immune proteins normally generated to fight illness or infection — that bind to and interfere with brain cells. These antibodies have been identified in the blood of some mothers of ASD children. Mothers are protected from these antibodies by the blood-brain barrier, but embryos may be vulnerable before the barrier has formed.

For this study, the authors isolated several such antibodies from mothers of ASD children and injected them into pregnant mice at a time in fetal development when the brain was unprotected from antibodies. "We found that male offspring but not female offspring exposed *in utero* to one particular antibody showed structural abnormalities in the developing brain," said lead author Lior Brimberg, PhD, of the Feinstein Institute for Medical Research in Manhasset, N.Y. "As adults, those male mice displayed behavioral abnormalities reminiscent of ASD."

The researchers determined that the antibody attacks a protein on the membrane of brain cells that is key to neuronal function. In previous studies, the gene for that same protein had been linked to ASD, and the deletion of this protein in mice has been shown to lead to ASD-like behaviors.

"Our finding that a single maternal anti-brain antibody mediates fetal brain abnormalities and long-term behavioral changes provides new insight into ASD," Brimberg said. "Our study could lead to development of reagents that block these antibodies and prevent the occurrence of this subtype of ASD."

This research was supported with funds from the Simons Foundation and the Department of Defense. Brimberg is also a NARSAD young investigator grantee.

Scientific Presentation: Wednesday, Oct. 21, 8-9:45 a.m., N230

655.01, Probing the contribution of maternal antibodies to autism spectrum disorder
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TECHNICAL ABSTRACT: Maternal brain-reactive antibodies have been associated with increased risk for Autism Spectrum Disorders (ASD) in the offspring. This is due to the fact that maternal brain-reactive antibodies can affect the fetal brain before the development of a competent blood brain barrier that prevents exposure to antibody. Several studies have indicated that mothers with an ASD child have significantly higher levels of anti-brain antibodies in the serum compared to mothers of typically developed children and women of child bearing age. Previous studies have used polyclonal serum to study maternal antigenic specificities, and their postnatal effects. We developed a method to generate monoclonal brain-reactive antibodies to study the antigenic specificities of brain-reactive antibodies and to determine which contribute to ASD pathogenesis. We show in a mouse model that exposure in-utero to a monoclonal brain-reactive antibody isolated from a mother of an ASD child induces neurodevelopmental effects in the offspring that can be observed already during the embryonic stage. We identified brain-reactive B cells in blood of women with brain-reactive IgG and a child with ASD and generated monoclonal (Mab) brain-reactive antibodies by single cell cloning and expression. One Mab, C6 was found to target Caspr2, a protein that is part of the voltage gated potassium channel complex and is encoded by a known autism associated gene. When this Mab was administrated to pregnant mice at E13, male but not female mice showed thinning of the cortical plate and fewer mitotic cells at E15 compared to embryos of mice injected with a non brain-reactive Mab. Two-week-old mice showed reduced dendrite complexity in the CA1 region of the hippocampus, which continued into the adulthood. Adult mice also showed reduced GABAergic neurons in the same region. In parallel, in adulthood, male mice exposed to C6 showed increased stereotypic behavior, reduced sociability and inflexibility in a learning paradigm. This work demonstrates that anti-brain antibodies cloned from a mother of an ASD child lead to in -vivo to structural and behavior alterations. Identifying pathogenic brain-reactive Mabs may translate into future protection studies.

Abstract 42.03 Summary

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Huntington's Disease Alters Development of Brain Circuitry During Childhood

Imaging reveals weakened connections between key regions controlling motor functions, emotions

Although symptoms of Huntington's disease do not appear until well into adulthood, brain circuitry changes are detectable during childhood, according to research released today at Neuroscience 2015, the annual meeting of the Society for Neuroscience and the world's largest source of emerging news about brain science and health. The new insights into the earliest stages of Huntington's disease could guide the development of future treatments — particularly when and where to deliver them.

Huntington's disease is characterized by jerky, uncontrolled movements and causes cognitive and emotional disturbances. Huntington's is an inherited neurologic disorder caused by a mutation in an autosomal dominant gene, meaning children of a parent with Huntington's have a 50 percent chance of developing the fatal disease. The affected gene normally encodes a protein called huntingtin (HTT), which is present in the brain throughout life, including during development. In Huntington's disease, this gene is mutated and encodes a mutated form of HTT. Scientists have long wondered how the presence of the mutant protein affects brain development before symptoms appear.

The gene marker makes it possible to study patients before the onset of symptoms. Researchers from the University of Iowa used resting-state functional magnetic resonance imaging (rs-fMRI) to compare the brains of 26 children who harbored the gene mutation with the brains of 36 healthy children. Brain areas that work together are known to exhibit spontaneous synchronous activity — meaning the neurons fire together, even when the brain is not engaged in a specific activity. Stronger co-activity during rest is thought to reflect stronger functional connections between the areas when they are actively engaged. By measuring this resting synchronous activity, the researchers determined that the children with mutant HTT showed weaker functional connectivity between striatal and cortical brain structures, circuits that govern motor and emotional controls. Interestingly, other areas were more strongly connected in the pre-disease children, suggesting a possible compensatory effort by the brain.

"The results suggest that lifelong possession of the genetic mutation for Huntington's affects the coordinated development between the striatum and frontal lobe during childhood," said lead author Jessica Lee, PhD. The work offers new clues to how the Huntington's-affected brain works long before symptoms arise. Further study "could help determine the most effective timing and target area in the brain to intervene prior to any irreversible structural degeneration," Lee added.

Research was supported with funds from the National Institute of Neurological Disorders and Stroke and the CHDI Foundation.

Scientific Presentation: Saturday, Oct. 17, 3-4 p.m., Hall A

42.03, Altered striatal resting state functional connectivity in children at risk for Huntington's disease.
***J. LEE**[1], E. AXELSON[1], J. BRUSS[1,2], V. MAGNOTTA[3], P. NOPOULOS[1,2,4];
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TECHNICAL ABSTRACT: Background: Huntington's disease (HD) is an autosomal dominant disease caused by an expansion of the CAG repeats on the gene encoding for the huntingtin protein (HTT). The dysfunction of the striatum which shows selective vulnerability to mutant huntingtin (mHTT), is known to underlie the characteristic HD symptom manifestation. Although the primary neuropathology is that of neurodegeneration of the striatum, the presence of mHTT throughout the life span may also affect normal maturational processes and circuit formation of the striatum that take place during development. Objective: In the current study, the effect of mHTT on striatal functional integrity was examined by evaluating resting-state functional magnetic resonance imaging (rs-fMRI) data in children (6-18 years of age) who are at risk for HD (no juvenile HD included). Method: Using seed-based analyses of the rs-fMRI data, the functional connectivity of the striatum in children tested as gene-expanded (n=26, CAG repeats ≥ 40) as a result of presymptomatic gene assessment (for research purposes only) were compared to that of 36 healthy children. Results: Compared to healthy peers, the gene-expanded children showed significantly weaker correlational strength between 1) the putamen and the motor cortex and 2) the ventral striatum and the anterior cingulate cortex. However, the gene-expanded children also exhibited significantly stronger functional coupling between 1) the caudate and the anterior prefrontal cortex, 2) the putamen and the superior frontal gyrus and 3) the ventral striatum and orbitofrontal cortex, when compared to healthy controls. Conclusions: The decreased functional synchronization between the striatum and associated frontal lobe areas in the gene-expanded children, indicate aberrant striatal functionality directly linked to mHTT. Interestingly, these decrements coincided with increased functional connectivity along the fronto-striatal circuitry which may reflect a potential compensatory mechanism. The results suggest that lifelong possession of mHTT could alter the striatum's intrinsic functional architecture, decades ahead of HD diagnosis. Importantly, understanding how the brain dynamically copes with such persistent effect of mHTT may help determine the most effective timing and target area to intervene prior to any irreversible structural degeneration.