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Impact of Maternal Obesity on Fetuses' and Children's Neurodevelopment

March 15th, 2023

Dr. Lynne Ausman | Dr. Tomo Tarui

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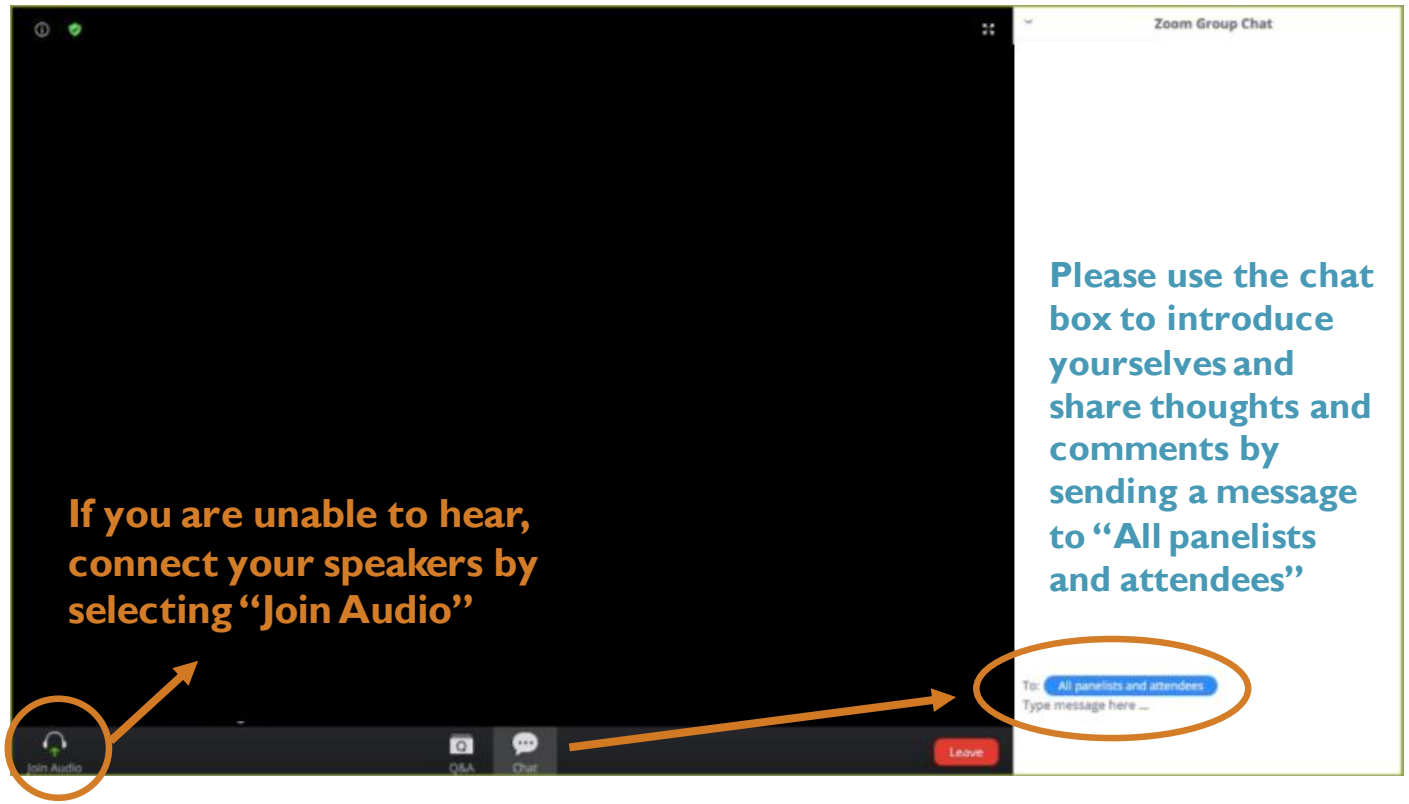
WELCOME TO THE ZOOM WEBINAR



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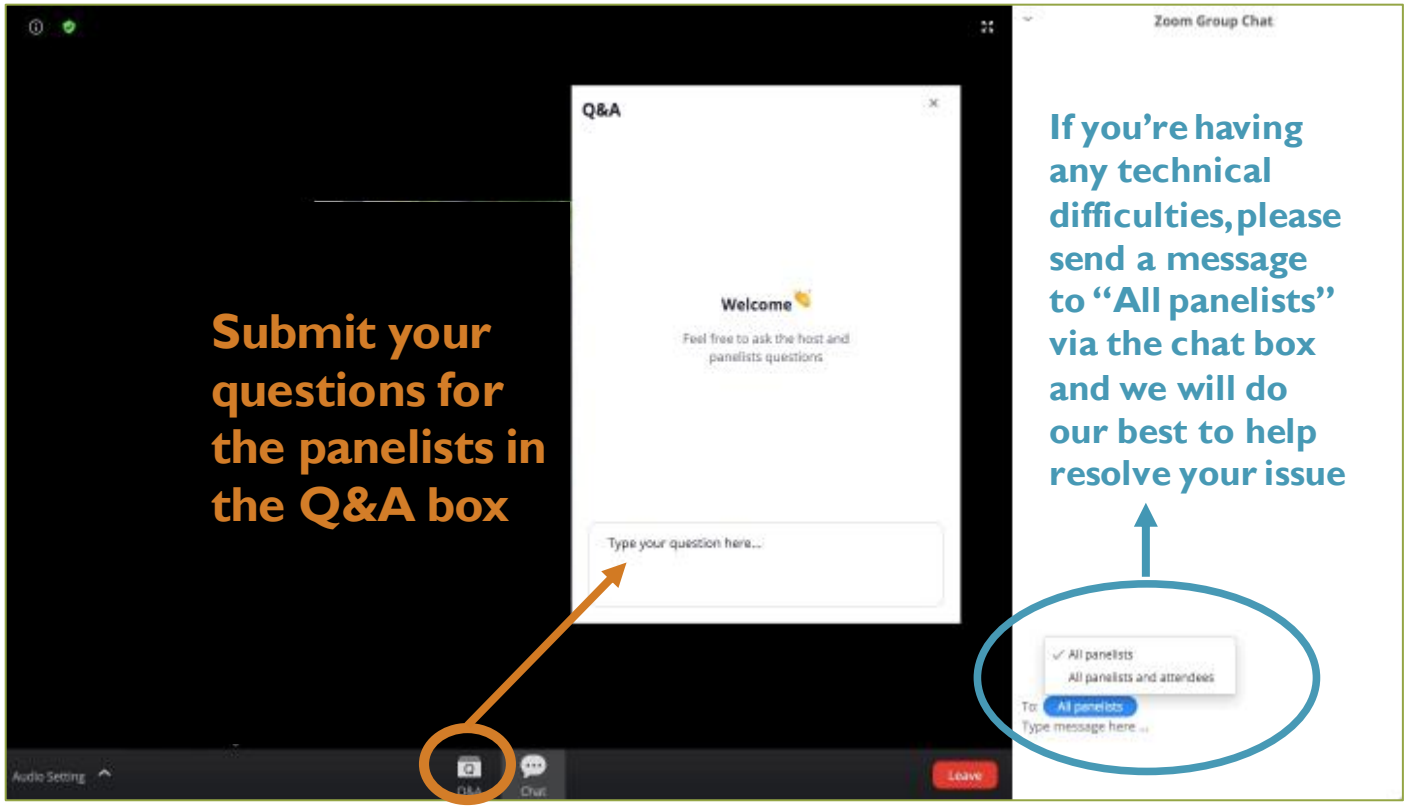
Q&A AND CHAT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Jordan Nutrition Innovation Lab Webinar

Impact of Maternal Obesity on Fetuses' and Children's Neurodevelopment

Wednesday, March 15th, 2023
3:30-4:30 pm Jordan Time | 7:30-8:30 am US Eastern

LYNNE AUSMAN
Tufts University

TOMO TARUI
Hasbro Children's Hospital

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Tufts UNIVERSITY | Gerald J. and Dorothy R. Friedman School of Nutrition Science and Policy

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Impact of maternal obesity on fetuses' and children's neurodevelopment

Tomo Tarui, MD
Director, Fetal Neonatal Neurology, Pediatric Neurology
Hasbro Children's Hospital, Women & Infants Hospital
Assistant Professor of Pediatrics and Neurology
The Warren Alpert Medical School of Brown University

March 15, 2023

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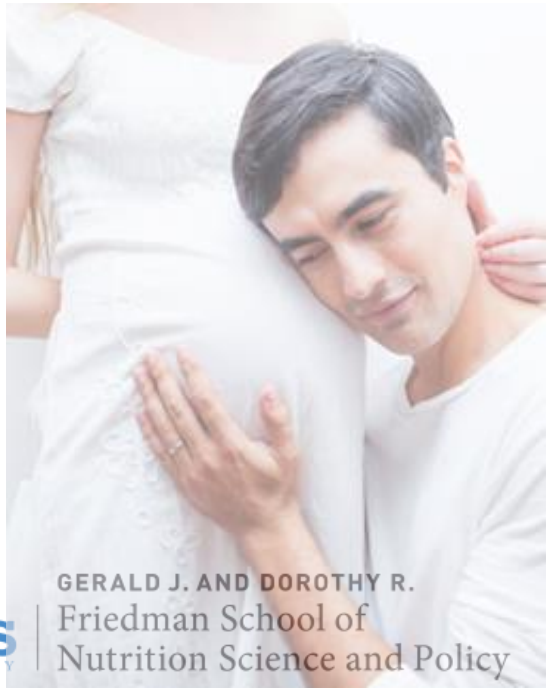
DISCLOSURE

- No relevant financial relationships have been reported in the past 24 months with an ACGME-defined ineligible company.
- I won't be discussing off-label uses for purposes other than that for which the food and drug administration (US) approved the product use.
- I will discuss the investigative analysis of fetal brain MRI beyond clinical practice.

OVERVIEW

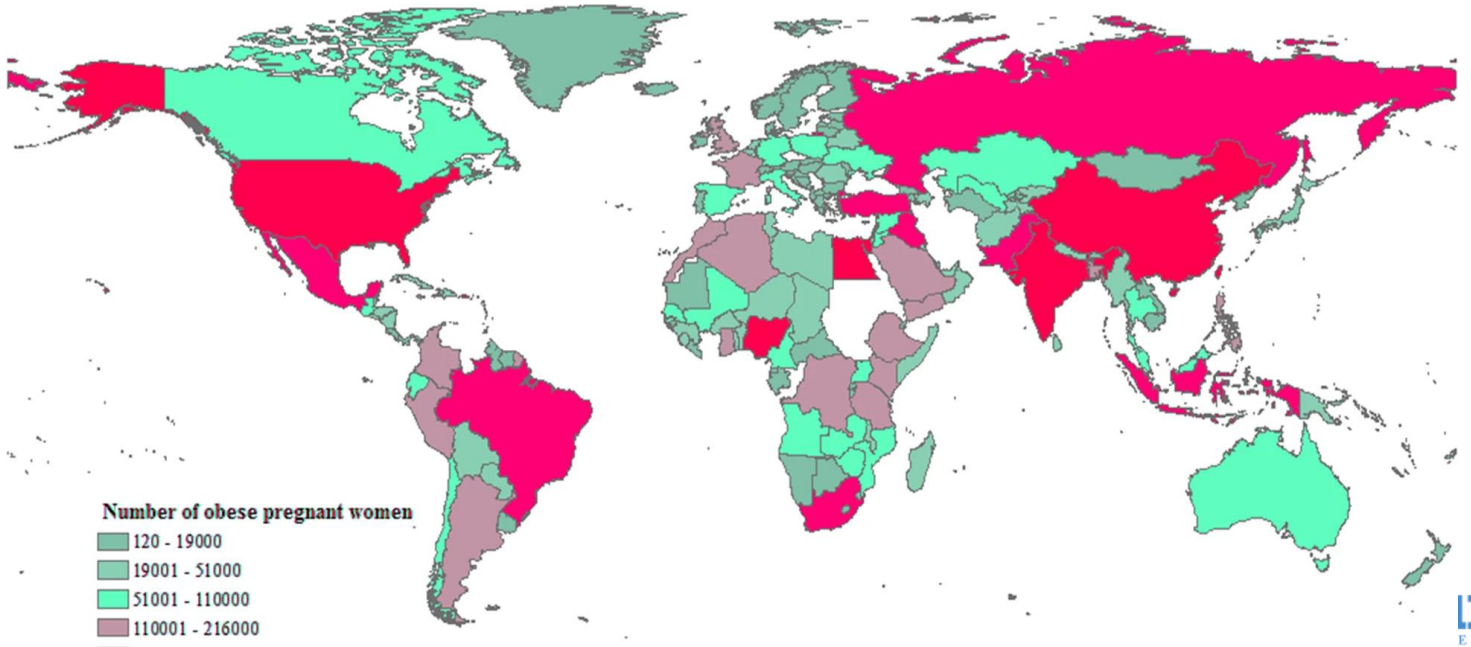
1. Impact of maternal obesity pregnancy on offspring children's neurodevelopment
2. How to assess the living fetal brain?
3. Preliminary data on the altered fetal brain development of fetuses of pregnant women with obesity



OBESITY PREGNANCY

- Maternal obesity [pre-pregnancy body mass index (BMI) ≥ 30 kg/m2] is an epidemiological public health risk all over the world (US 29%).
- Maternal obesity has transgenerational health impacts on their offspring children's health.

The estimated distribution of obese pregnant women—the global perspective (184 countries, 2014)



Chen et al. 2018
Strauss, 2021

NEURODEVELOPMENTAL IMPACTS OF MATERNAL OBESITY

- Offspring children of maternal obesity pregnancy have increased risks of cardiovascular, metabolic, neurodevelopmental, and psychiatric disorders.
- Large-scale national registry studies reported that maternal obesity increases the risk of various neurodevelopmental disorders (NDD) in offspring
  - Attention Deficit Hyperactivity Disorder (ADHD): + 47~89% risk
  - Autism Spectrum Disorder (ASD): 1.5~2-fold risk
  - Anxiety and depression

ADHD

- Prevalence: Jordan: 6.2 ~ 40.6% (Nafi et al. 2011, Al Azzam et al. 2016), US: 8-10%
- ADHD manifests as hyperactivity, impulsiveness, and poor attention, resulting in impairments in working memory, executive function, and impulsive behaviors.
- Causes: Genetics? Environmental?
- Four Nordic birth cohort studies found that maternal body mass index (BMI) dose-dependently increases the risk for children's ADHD symptoms. Excessive gestational weight gain increases risk.

Severity of maternal obesity	% Increased risk of ADHD in children
Overweight (BMI 25 ≤, <30)	+ 23~28%
Obesity (BMI 30 ≤, <35)	+ 47~89%
Severe obesity (BMI ≥ 35)	+ 88~95%

Rodriguez et al. 2008, Chen et al. 2014, Anderson et al. 2018, Kong et al. 2018

AUTISM SPECTRUM DISORDER (ASD)

- Prevalence: Jordan: ?, UAE 0.29% (29/10,000, Eapen et al. 2007), Oman 0.14% (1.4/10,000, Al-Farsi et al. 2011), US 2.3% (1/44, ADDM Network). **Diagnostic factor.**
- ASD manifests as difficulties in communication and interaction with other people, restricted interest, and repetitive behaviors (DSM-V, NICHD)
- Causes: Genetics? Environmental?
- Pre-pregnancy obesity increases the odds ratio for ASD in offspring by 1.3~2.05 -fold
- Excessive gestational weight gain also increases the risk for ASD in children by 10~58%

ALTERED BRAIN DEVELOPMENT IN OFFSPRING OF WOMEN WITH OBESITY

- Offspring children of maternal obesity pregnancy had structural and functional alterations in brain
  - Smaller hippocampus in school age boys (but not in girls) (Alves et al. 2020)
  - Altered white matter integrity (higher fraction anisotropy and lower mean diffusivity) in children and adults (Verdejo-Roman et al. 2019)
- Intrauterine origin? (Neonatal brain study)
  - Poorer white matter maturation in newborns (Ou et al. 2015)
  - Decreased functional connectivity in the dorsal anterior cingulate cortex (Li et al. 2016)
- **Information on fetal brain development is lacking**

MOUSE AND RAT STUDY

- Animal (mouse, rat) models of diet-induced obesity during pregnancy
- Maternal obesity affects offspring's intrauterine brain development
  - Increased neuroprogenitor proliferation
  - Altered neuronal differentiation and maturation
  - Altered DNA methylation patterns
- Mechanisms
  - Altered lipid metabolism
  - Inflammation
  - Oxidative stress

Information on human fetal brain development is lacking

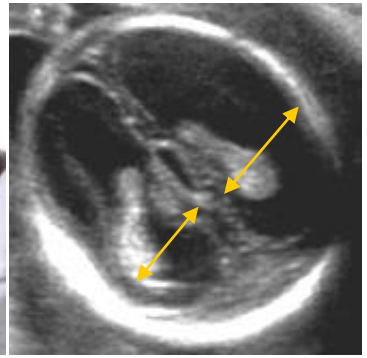
Chang et al. 2008, Niculescu et al. 2009, Stachowiak et al. 2014, Grissom et al. 2015

ASSESSING HUMAN BRAIN

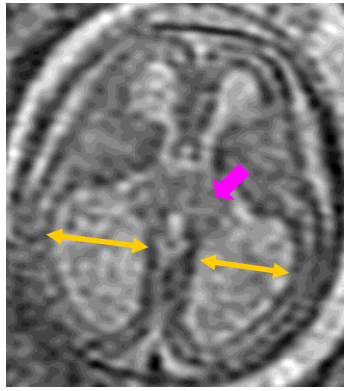
Current clinical practice

Anatomic Diagnosis

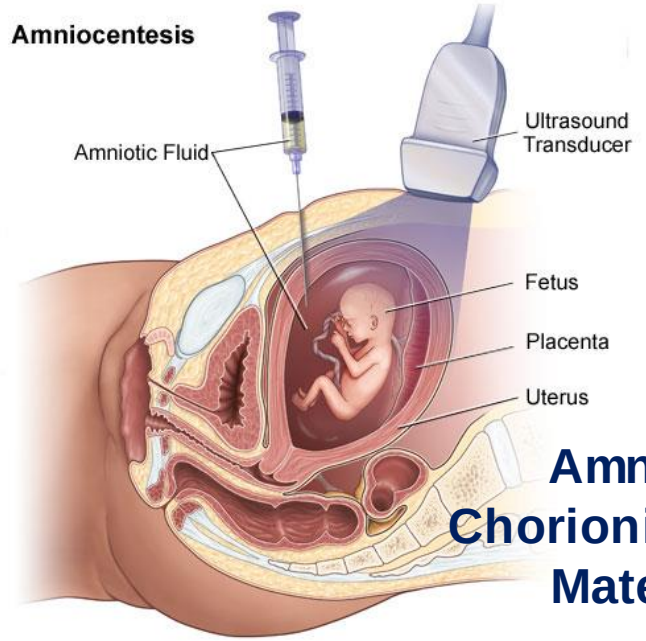
US



MRI



Genetic Diagnosis



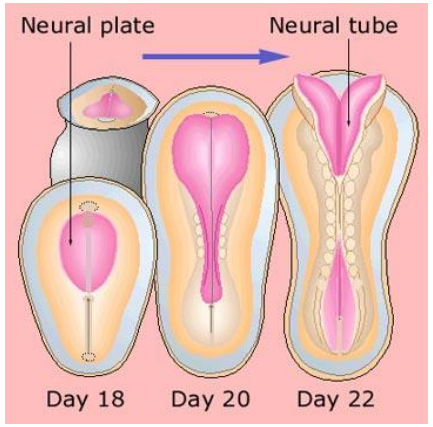
Amniocentesis
Chorionic villi sampling
Maternal blood

L1CAM muation+: c.2014 C>T point mutation resulting Q(Gln)672X (stop codon mutation)

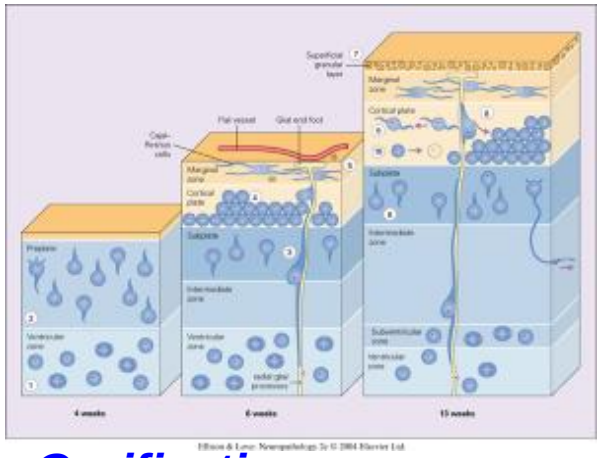
DYNAMIC DEVELOPMENT OF FETAL BRAIN

VULNERABLE OR POTENTIAL?

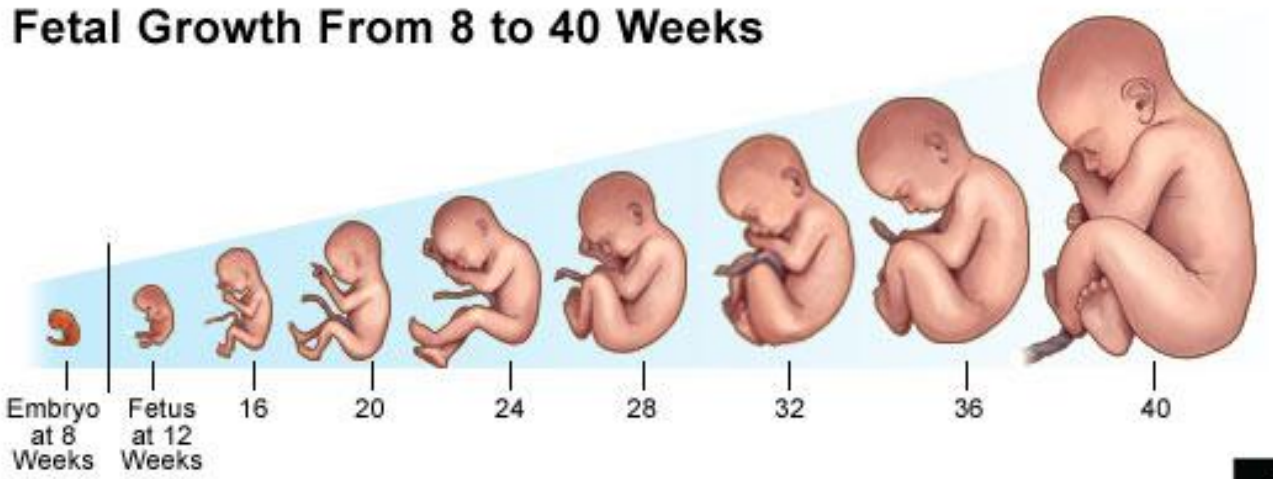
Neurulation

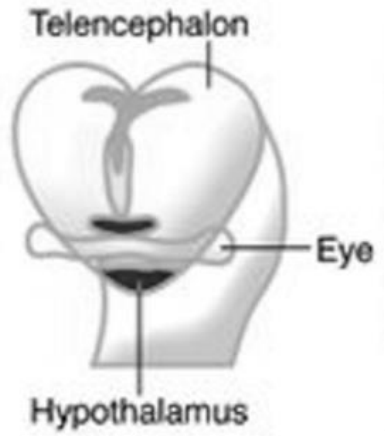


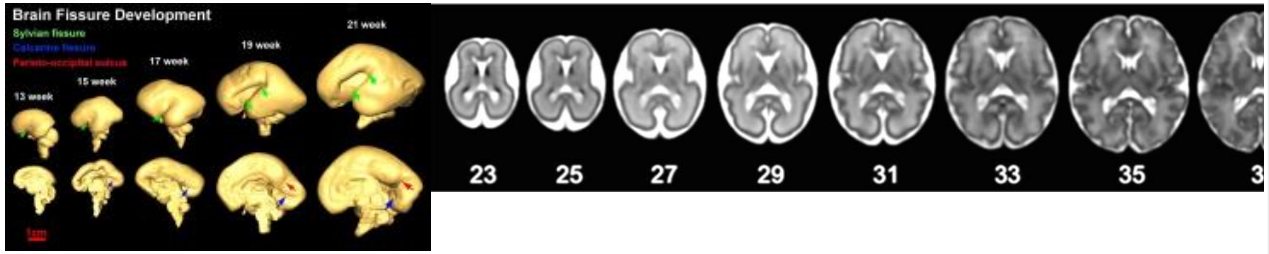
Neurogenesis, Migration

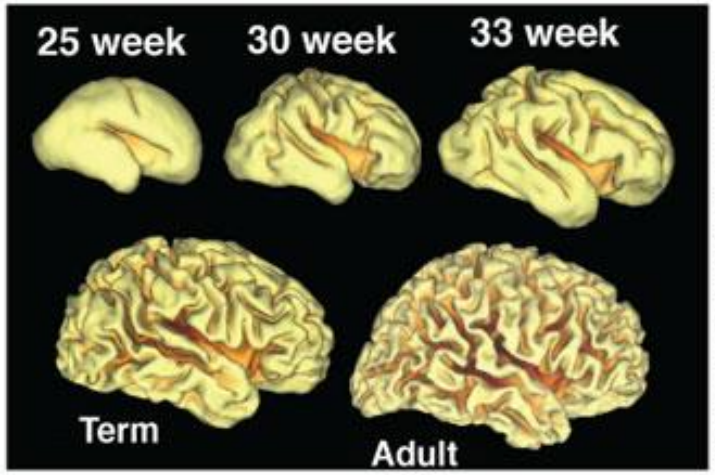


Gyrification,
Sulcal development









https://embryology.med.unsw.edu.au/embryology/images/, http://www.ifindproject.com/

Midline formation
(Segmentation, Regionalization)

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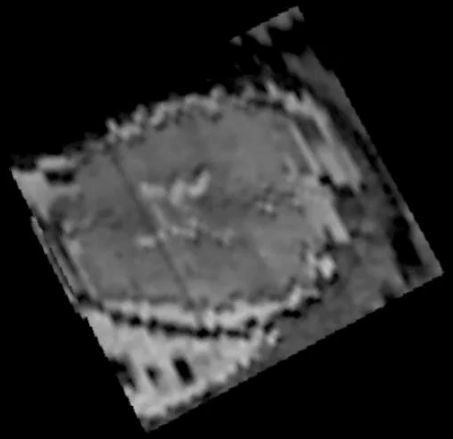
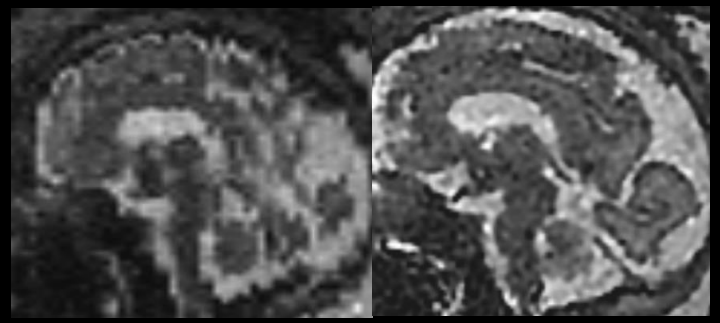
Novel fetal MRI technology

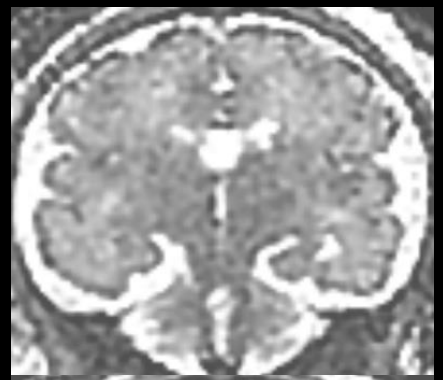
- *Quantitative analysis of fetal brain MRI*

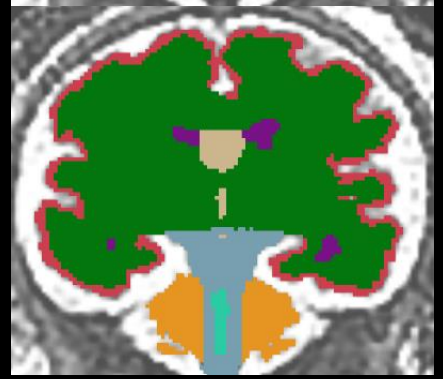
Artifact correction



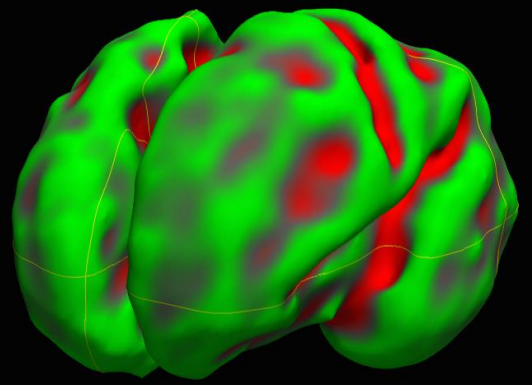


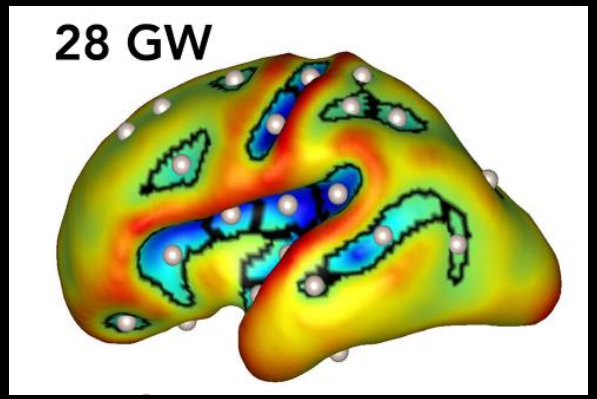
Segmentation Volumetric analysis





3D cerebral surface analysis





Maria Murgasova, Oxford

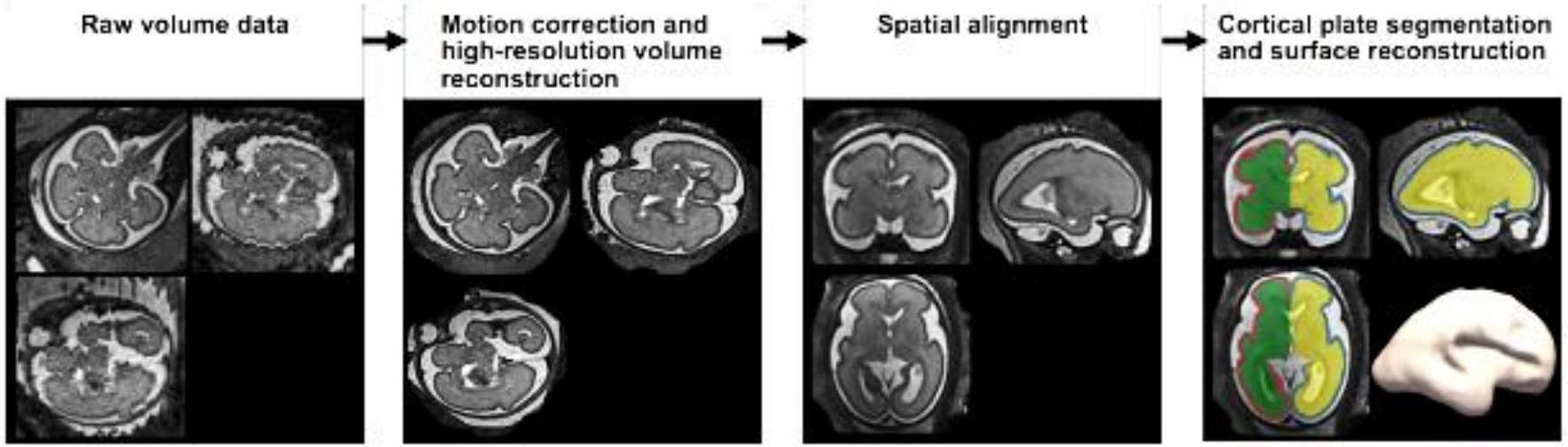
DETERMINE IMPACT OF MATERNAL OBESITY ON REGIONAL FETAL BRAIN GROWTH

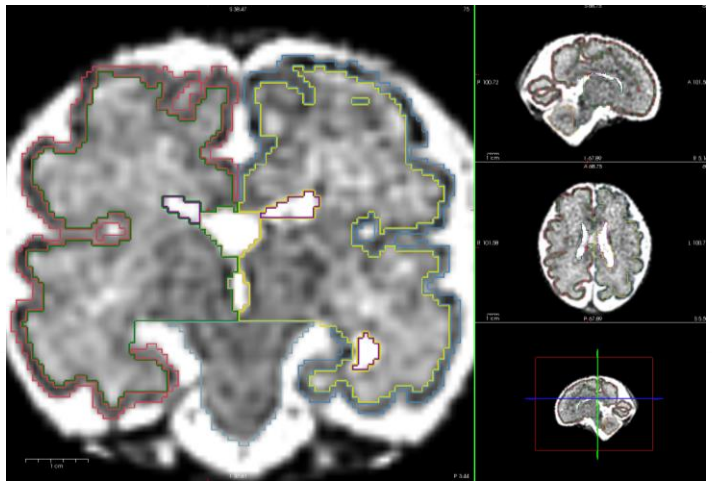
Emiko Takeoka, MD

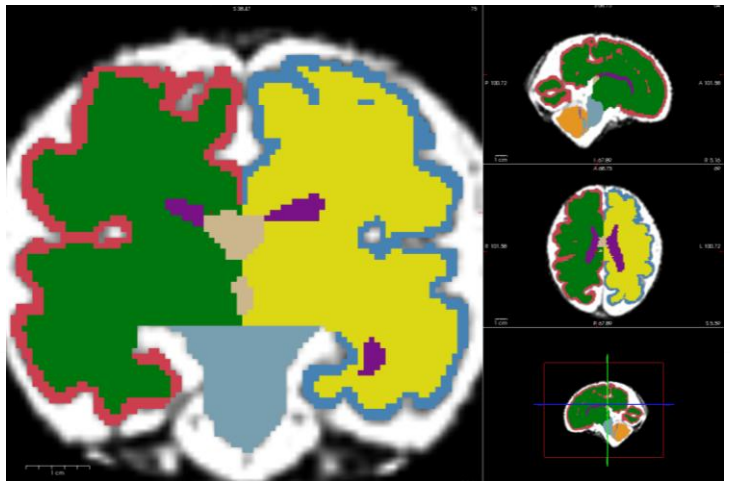
Perrie O'Tierney-Ginn

- Prospective observational study at Tufts Medical Center
  - Inclusion: Healthy pregnant women aged 15 to 45, singleton pregnancy, gestational week between 18 and 36, and both fetal sexes
  - Exclusion: Multiple pregnancies, abnormal fetal sonographic findings or MRI findings, or known chromosomal abnormalities
- Offered research fetal brain MRI scans
- Segmentation and Volumetric analysis using Freeview.
- Statistical analysis: Comparison of non-linear growth regression models between BMI groups.

BRAIN REGIONAL VOLUMETRIC ANALYSIS OF FETAL BRAIN

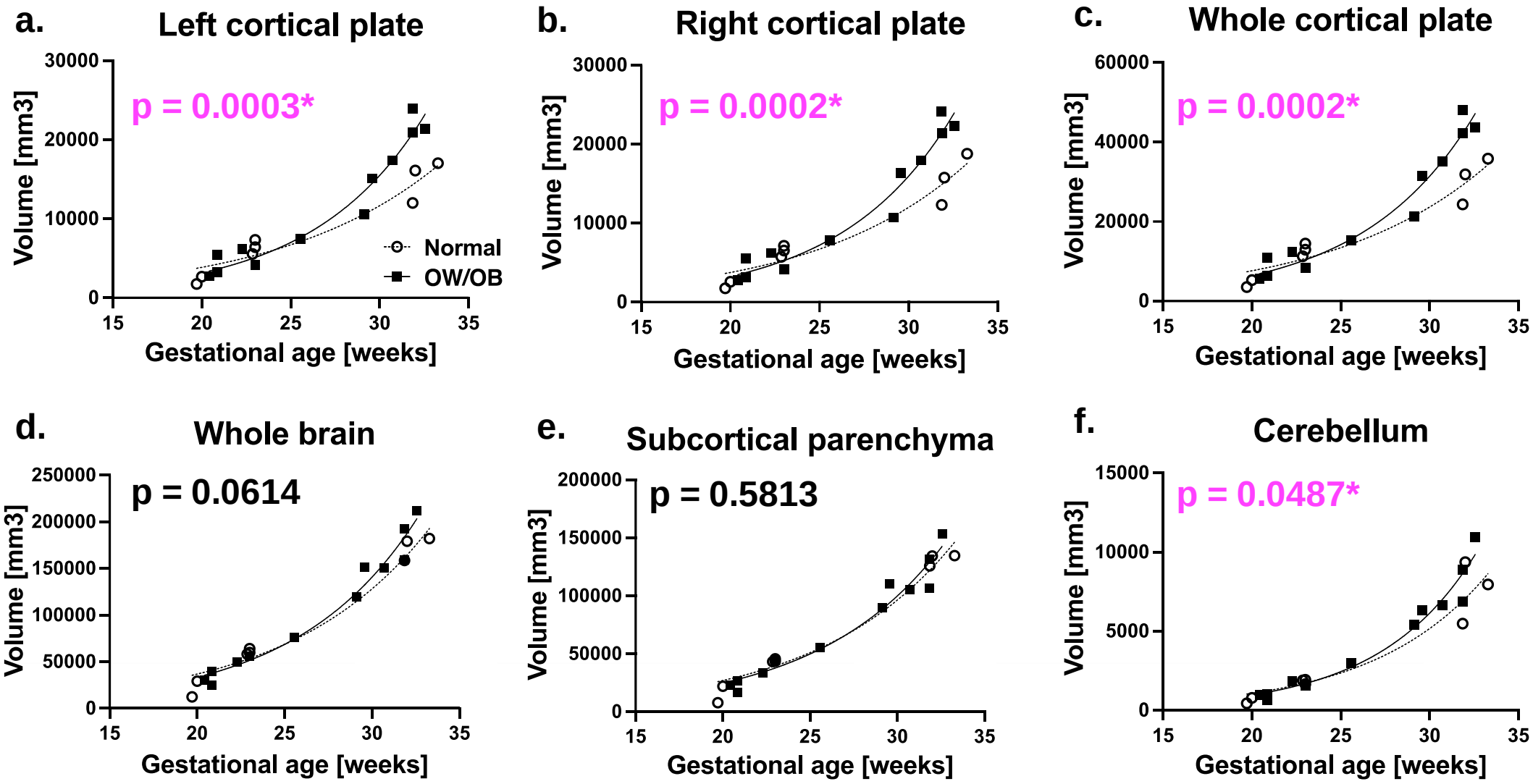






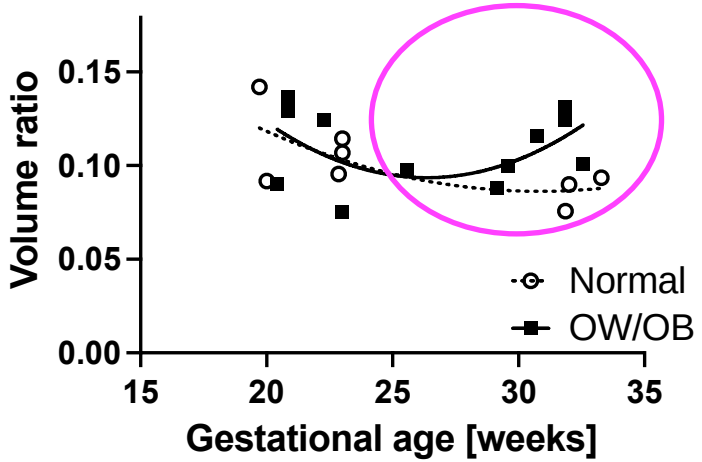
- Right cortical plate
- Left cortical plate
- Right subcortical parenchyma
- Left subcortical parenchyma
- Cerebellar hemispheres
- Cerebellar vermis
- Lateral ventricles
- IIIrd ventricle
- Brainstem

ACCELERATED FETAL BRAIN GROWTH IN MATERNAL OBESITY PREGNANCY

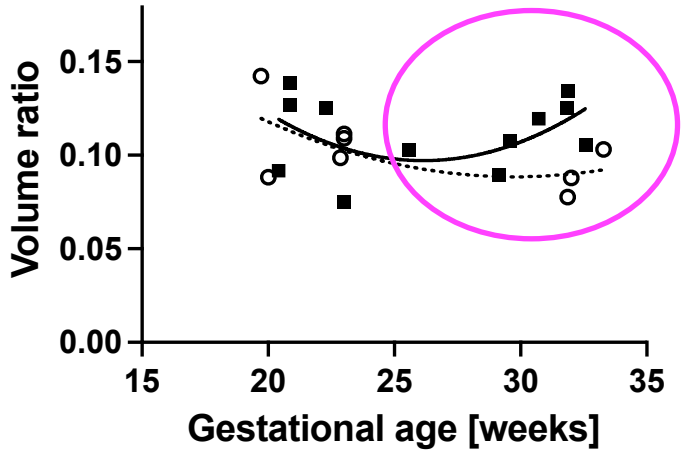


CORTICAL PLATE IS SPECIFICALLY BIGGER RELATIVE TO WHOLE BRAIN

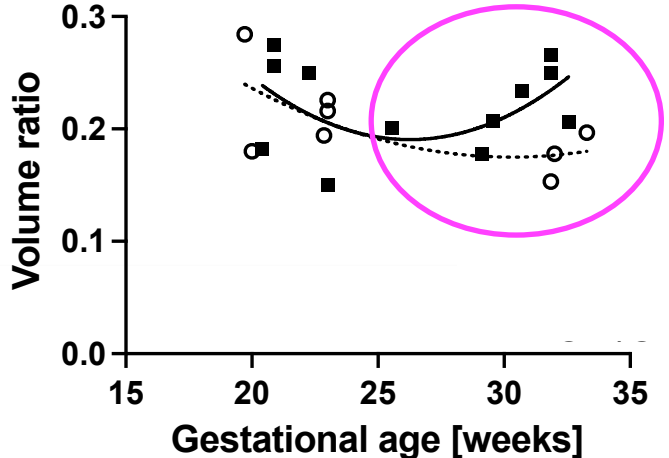
a. Left cortical plate / Whole brain



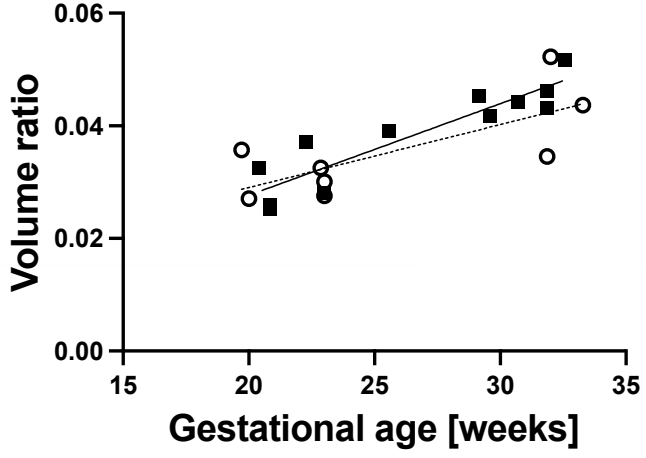
b. Right cortical plate / Whole brain



c. Whole cortical plate / Whole brain



d. Whole cerebellum / Whole brain



ACCELERATED FETAL BRAIN GROWTH IN PREGNANCY COMPLICATED WITH MATERNAL OBESITY

- Maternal high BMI had increased regional brain volume cortical plate and whole cerebellum
- Cortical plate is specifically increased volume compared to the rest of the fetal brain

Limitations

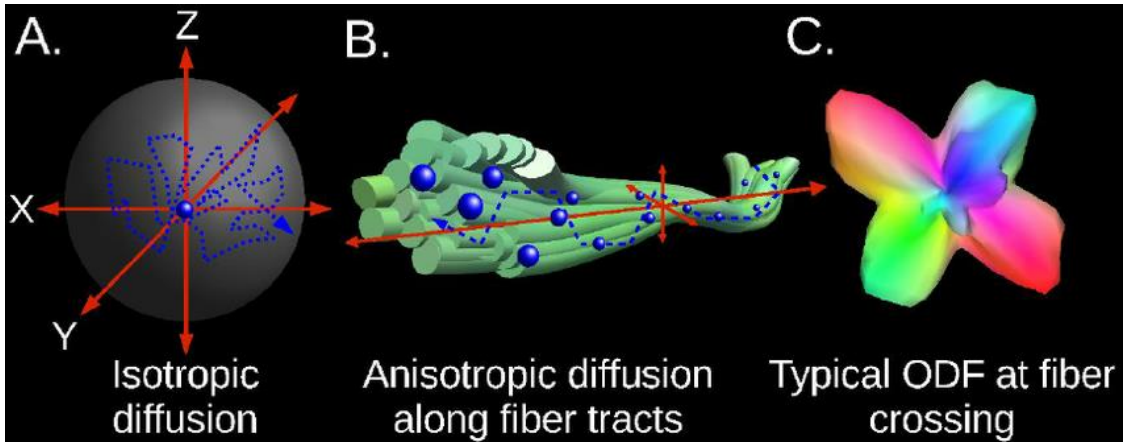
- Need larger cohort study
- Longitudinal analysis (fetal to neonatal brain development)
- Association with neurodevelopmental outcomes

  Infants/toddlers with ASD have larger brain

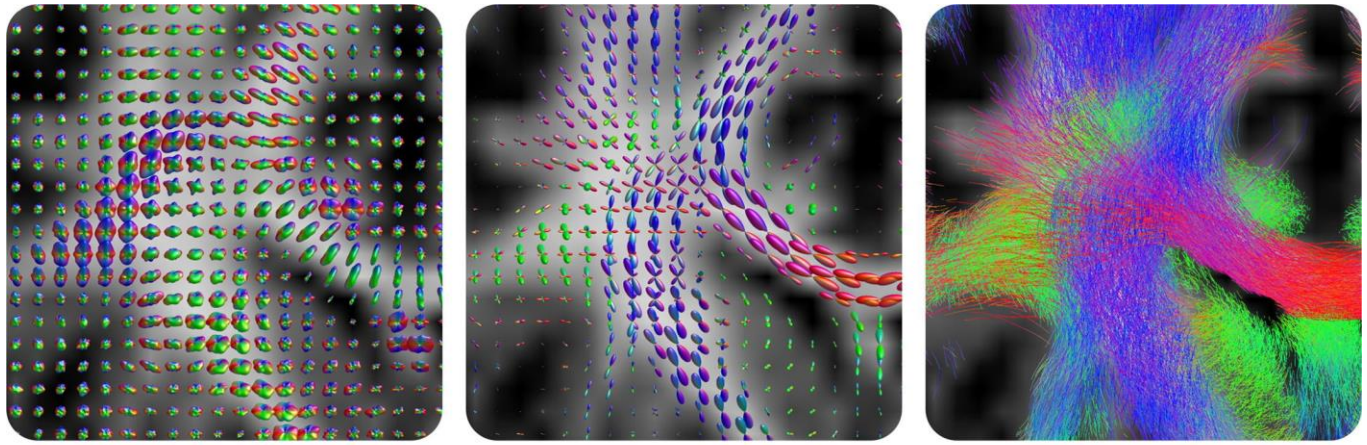
  Children and adults with ASD have altered connectivity, gyrification

FETAL BRAIN DIFFUSION MRI ANALYSIS - AXONAL, CONNECTION DEVELOPMENT

- Diffusion analysis
  - Apparent Diffusion Coefficient (ADC), Fraction Anisotropy (FA) analyses
  - Diffusion tensor imaging (DTI) analysis



Phillips et al, 2012



Reviewed in Tournier, 2019

RADIO-PATHOLOGICAL CORRELATION OF COMMISSURAL AND INTERNAL CAPSULE FIBERS

frontiers in Neuroanatomy

ORIGINAL RESEARCH
published: 24 December 2015
doi: 10.3389/fnana.2015.00164

CrossMark

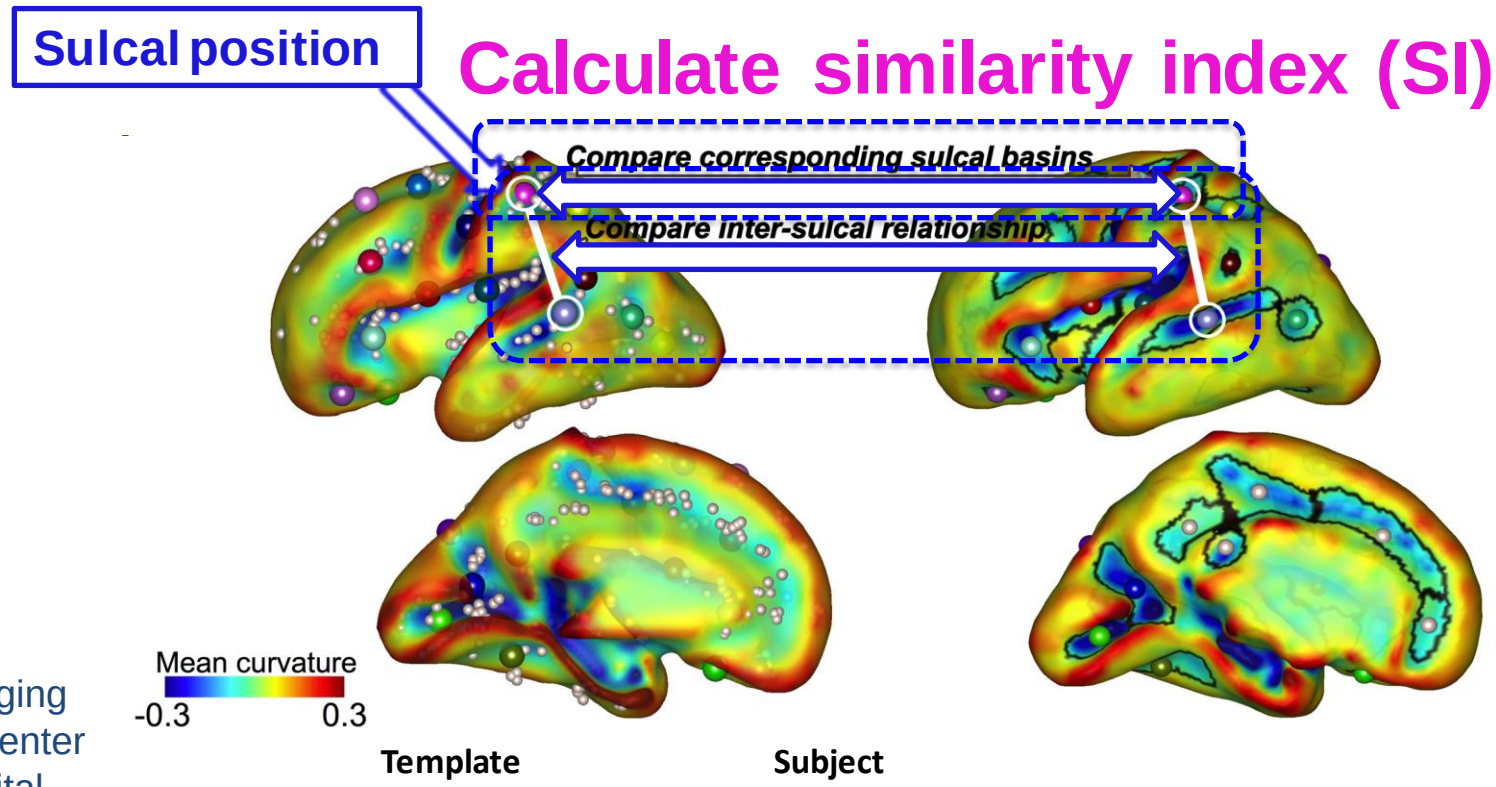
Validation of *In utero* Tractography of Human Fetal Commissural and Internal Capsule Fibers with Histological Structure Tensor Analysis

Christian Mitter[1,2], András Jakab[3], Peter C. Brugger[4], Gerda Ricken[2], Gerlinde M. Gruber[4], Dieter Bettelheim[5], Anke Scharrer[6], Georg Langs[3], Johannes A. Hainfellner[2], Daniela Prayer[1] and Gregor Kasprian[1]*

[1] Division of Neuroradiology and Musculoskeletal Radiology, Department of Biomedical Imaging and Image-guided Therapy, Medical University of Vienna, Vienna, Austria, [2] Institute of Neurology, Medical University of Vienna, Vienna, Austria, [3] Computational Imaging Research Lab, Department of Biomedical Imaging and Image-guided Therapy, Medical University of Vienna, Vienna, Austria, [4] Department of Systematic Anatomy, Center for Anatomy and Cell Biology, Medical University of Vienna, Vienna, Austria, [5] Division of Obstetrics and Feto-maternal Medicine, Department of Obstetrics and Gynecology, Medical University of Vienna, Vienna, Austria, [6] Clinical Institute for Pathology, Medical University of Vienna, Vienna, Austria

sue MRI,

SULCAL PATTERN MATCHING AND SIMILARITY ANALYSIS



Kiho Im, PhD
FNNDSC
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Fetal-Neonatal Neuroimaging
Developmental Science Center
Boston Children's Hospital

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FETAL CEREBRAL SURFACE ANALYSIS ISOLATED AGENESIS OF CORPUS CALLOSUM

OXFORD

Cerebral Cortex, 2017; 1–12

doi: 10.1093/cercor/bhx191
Original Article


Rie Kitano, MD


Alexa Craig, MD


Kiho Im, PhD

ORIGINAL ARTICLE

Disorganized Patterns of Sulcal Position in Fetal Brains with Agenesis of Corpus Callosum

Tomo Tarui[1,2,5,6], Neel Madan[7], Nabgha Farhat[1,2], Rie Kitano[5], Asye Ceren Tanritanir[1,2], George Graham[8], Borjan Gagoski[1,3], Alexa Craig[9], Caitlin K. Rollins[4], Cynthia Ortinau[10,11], Vidya Iyer[5], Rudolph Pienaar[1,3], Diana W. Bianchi[12], P. Ellen Grant[1,2,3] and Kiho Im[1,2]

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Fetuses with isolated agenesis of corpus callosum have altered sulcal position
Individual variations exist in sulcal positional patterns

Tarui, Kitano, Bianchi, Grant, Im et al. 2018

FETAL CEREBRAL SURFACE ANALYSIS REGIONAL ANALYSIS




HyuJin Yun, PhD

Kiho Im, PhD

Rie Kitano, MD

Shizuko Akiyama, MD PhD

- Cerebral cortex functional regionalization originates in fetal life

OXFORD

Cerebral Cortex, 2020;00: 1–11

doi: 10.1093/cercor/bhaa255
Original Article

ORIGINAL ARTICLE

Regional Alterations in Cortical Sulcal Depth in Living Fetuses with Down Syndrome

Hyuk Jin Yun[1,2], Juan David Ruiz Perez[1,2], Patricia Sosa[1,2], J. Alejandro Valdés[1,2], Neel Madan[3], Rie Kitano[4], Shizuko Akiyama[4], Brian G. Skotko[5], Henry A. Feldman[2,6], Diana W. Bianchi[7], P. Ellen Grant[1,2,8], Tomo Tarui[4] and Kiho Im[1,2]

[1]Fetal Neonatal Neuroimaging and Developmental Science Center, Boston Children's Hospital, Harvard Medical School, Boston, MA 02115, USA, [2]Division of Newborn Medicine, Boston Children's Hospital, Harvard Medical School, Boston, MA 02115, USA, [3]Department of Radiology, Tufts Medical Center, Boston, MA 02111, USA, [4]Mother Infant Research Institute, Tufts Medical Center, Boston, MA 02111, USA, [5]Down Syndrome Program, Genetics, Pediatrics, Massachusetts General Hospital, Boston, MA 02114, USA, [6]Institutional Centers for Clinical and Translational Research, Boston Children's Hospital, Harvard Medical School, Boston, MA 02115, USA, [7]Prenatal Genomics and Fetal Therapy Section, Medical Genetics Branch, National Human Genome Research Institute, Bethesda, MD 20892, USA and [8]Department of Radiology, Boston Children's Hospital, Harvard Medical School, Boston, MA 02115, USA

Fetuses with Down syndrome (DS) have regional specific altered sulcal depth

1, 2. Executive function
Multimodal processing

3. Auditory language and memory

4. Fine motor

5. Visuomotor processing

Developmental phenotype specific to children with DS

Yun, Kitano, Akiyama, Bianchi, Tarui, Im et al. 2020

SUMMARY

- Maternal obesity increases risk of offspring's ADHD or autism spectrum disorder by 1.5 to 2-folds
- Human brain imaging studies and animal model studies suggest intrauterine origin of altered fetal brain development
- Quantitative analysis of fetal brain MRI revealed that maternal obesity increased region-specific fetal brain growth
- Multimodal fetal brain MRI analysis can assess comprehensive human fetal brain development
- Understanding impact of maternal obesity on fetuses' and children's neurodevelopment may open doors for prevention/intervention

FATTY ACID AS A TREATMENT OF NEURODEVELOPMENTAL DISORDERS

- LCPUFAs have been thought to play critical nutritional roles in various neurodevelopmental and psychiatric disorders

ADHD

- Studies in children and adults with ADHD found lower n-3 LCPUFA blood levels (especially DHA). Milte et al., 2015; Antalis et al., 2006; Laasonen et al., 2009
- Nine randomized control trials since 2012 tested efficacy of LCPUFAs on ADHD symptoms
  - 7/9 studies reported some improved ADHD symptoms by various forms and contents of LCPUFAs supplements
    - Milte et al., 2012; Perera et al., 2012; Richardson et al., 2012; Widenhorn-Muller et al., 2014; Bos et al., 2015; Barragan et al., 2017; Dopfner et al., 2021

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