

Aging Gracefully: A Choline Case Study of Developmentally- Targeted Nutrition

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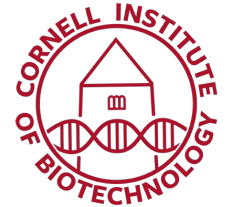
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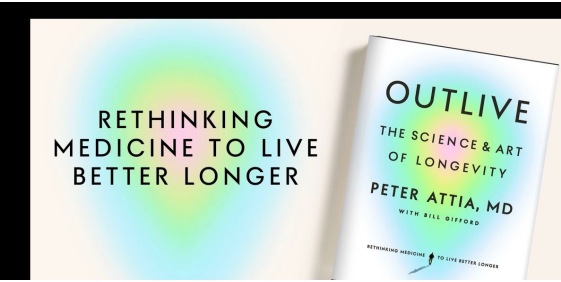


Talk Overview

- 1) Introduction to Aging, Geroscience and Nutrition
- 2) Windows of Opportunity
- 3) Choline Case Study
- 4) Wrap up



What do we mean by aging?

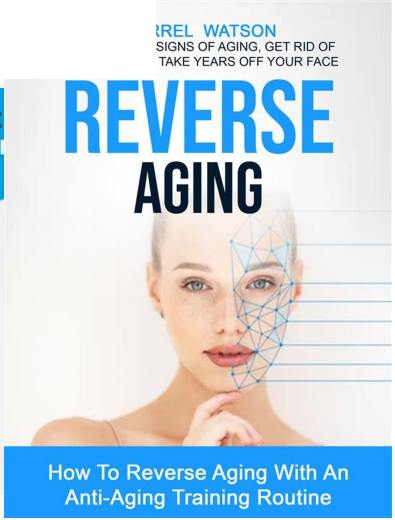


Cheese Protects You From All Causes Of Death, Says Science



10 Anti-Aging Foods to Support Your 40s-and-Beyond Body

Beautiful, glowing skin starts with how we eat, but these anti-aging foods can also help with more than that.



What Do We Mean by Aging?

Time since birth

**Chronological
Phenotype**

**Physical
Phenotype**

**Biological
Phenotype**

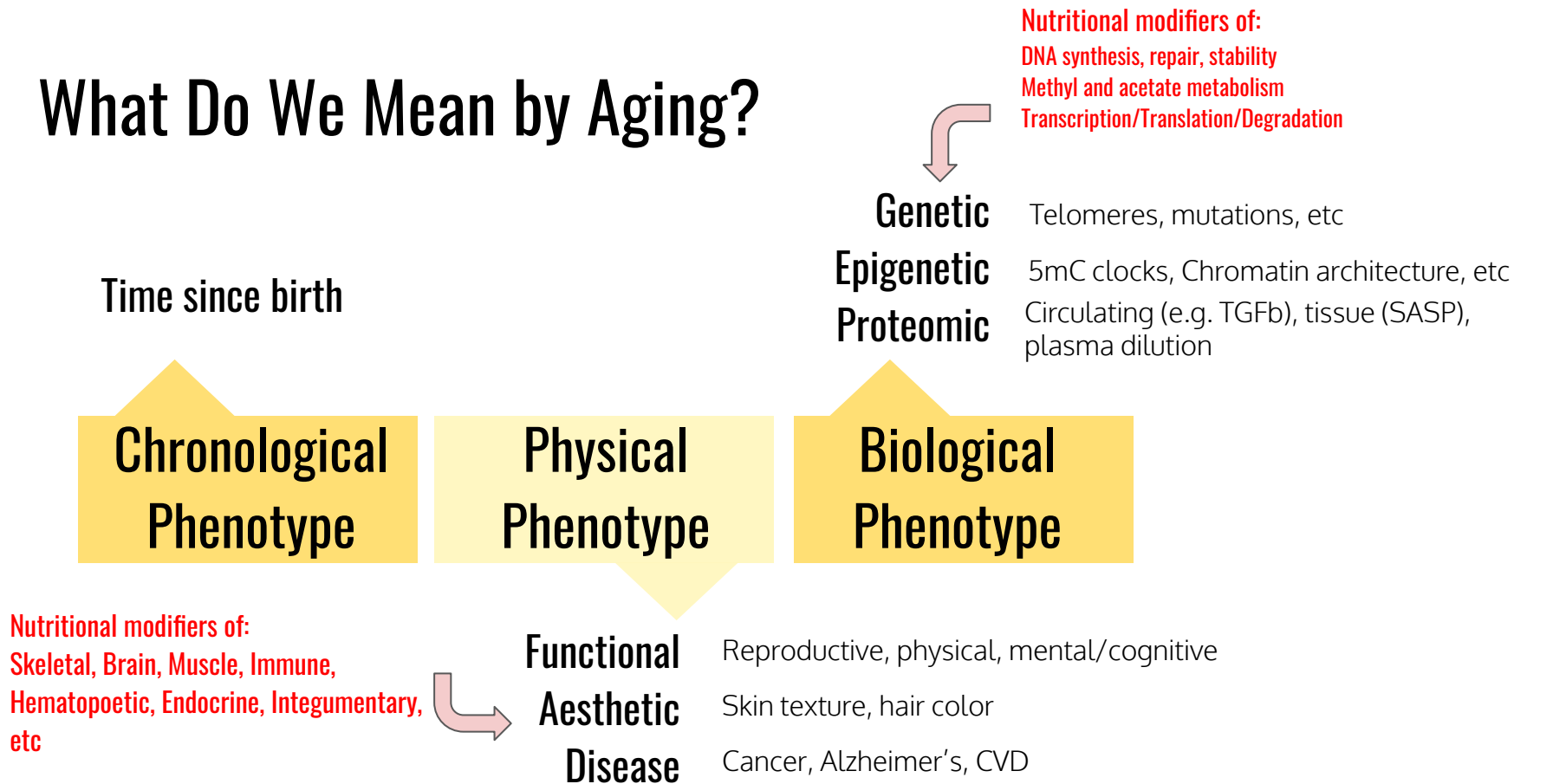
**Genetic
Epigenetic
Proteomic**

Telomeres, mutations, heteroplasmy etc
5mC clocks, Chromatin architecture, etc
Circulating (e.g. TGFb), tissue (e.g. SASP),
plasma dilution

**Functional
Aesthetic
Disease**

Reproductive, physical, cognitive, sensory
Skin texture, hair color
Cancer, Alzheimer's, CVD

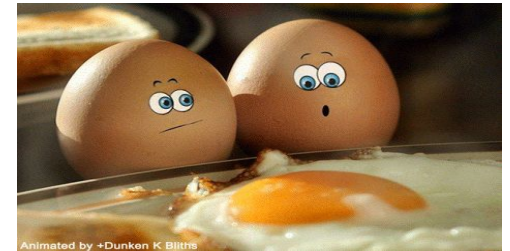
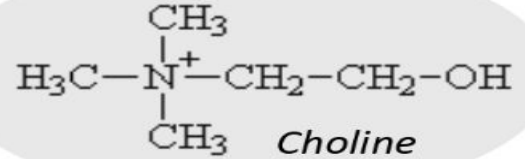
What Do We Mean by Aging?



...And where/when does nutrition make an impact?

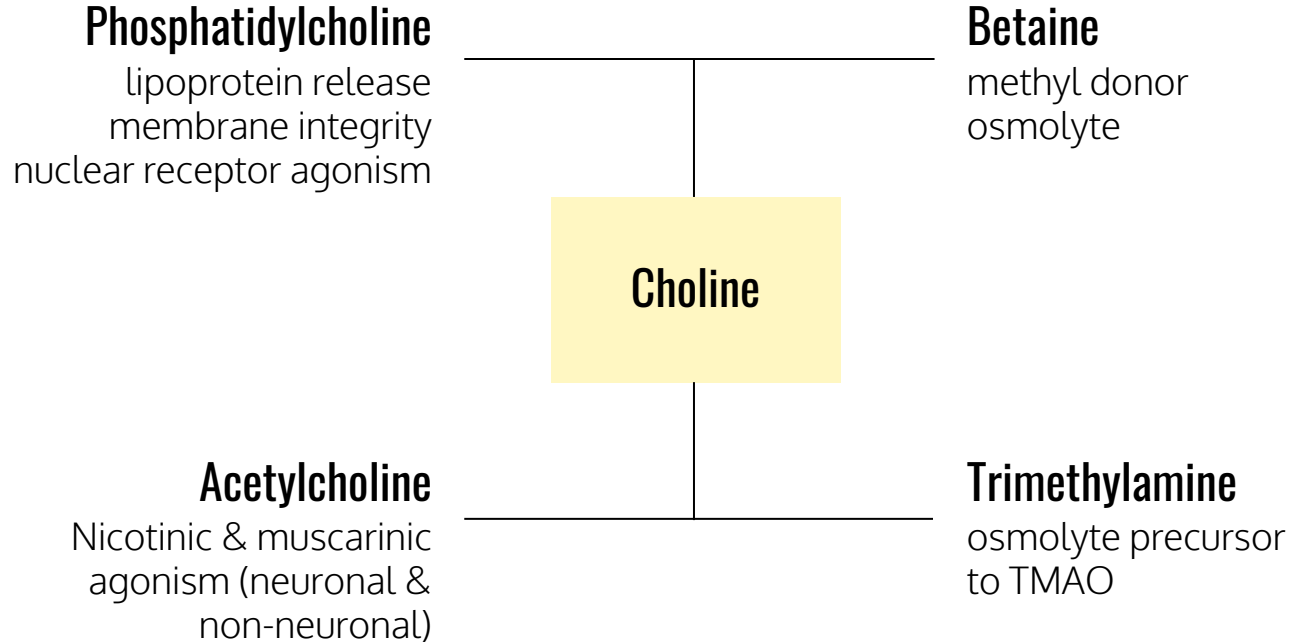
Early Life Nutritional Exposures: Choline

- Trimethylethanolammonium compound
- Water-soluble compound grouped with B-vitamins
- Deemed an essential nutrient in 1998 by the Institute of Medicine
 - Deficiency: fatty liver/ elevated LFTs
 - Controlled feeding/deprivation studies in men
 - Individuals undergoing long-term TPN
 - Adequate Intake Value established for **all life-stages**
 - Dietary choline represents a sum of 5 major water- & lipid-soluble choline-containing compounds

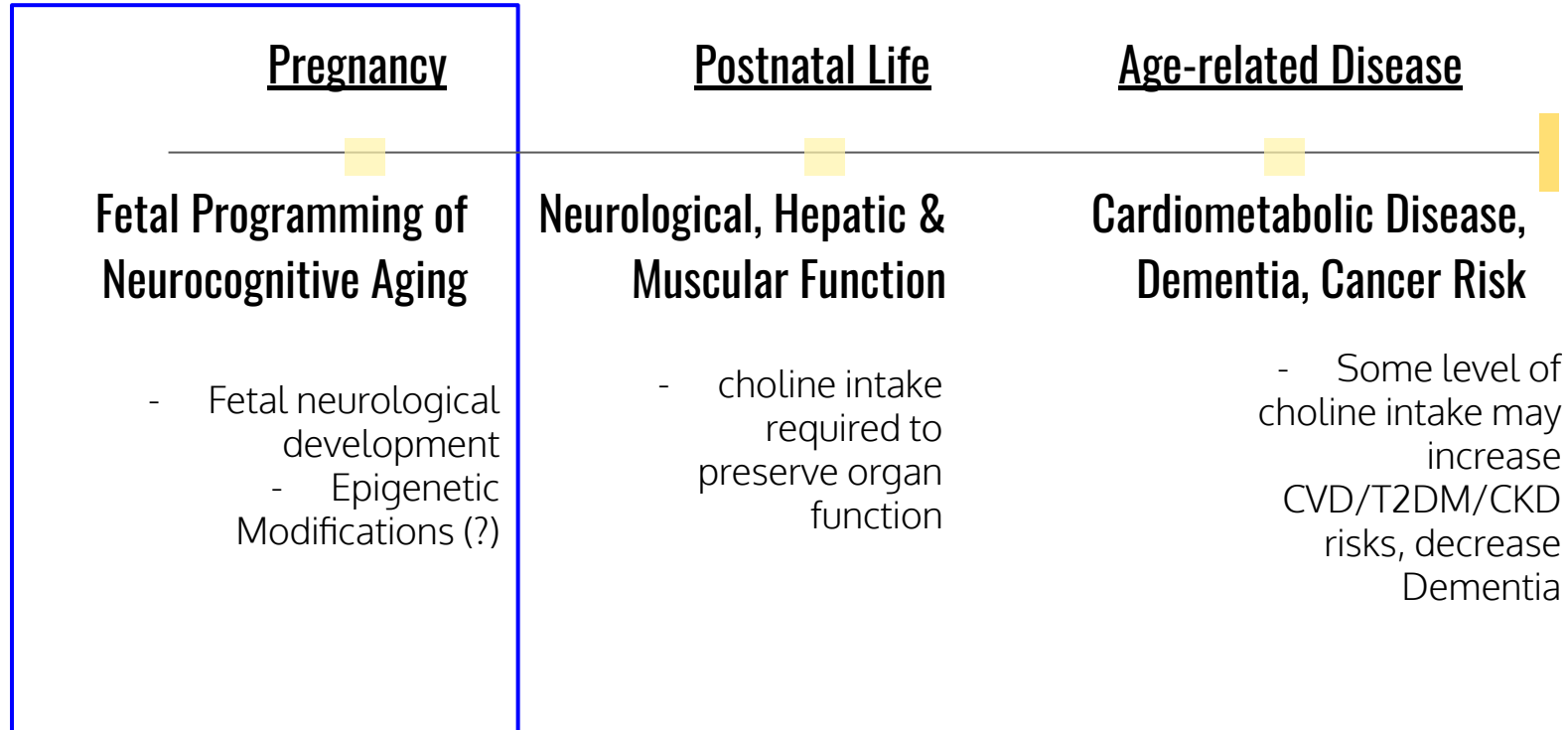


Institute of Medicine. Dietary reference intakes for thiamin, riboflavin, niacin, vitamin B6, folate, vitamin B12, pantothenic acid, biotin, and choline. Washington (DC): The National Academies Press; 1998.

Physiological Roles of Choline



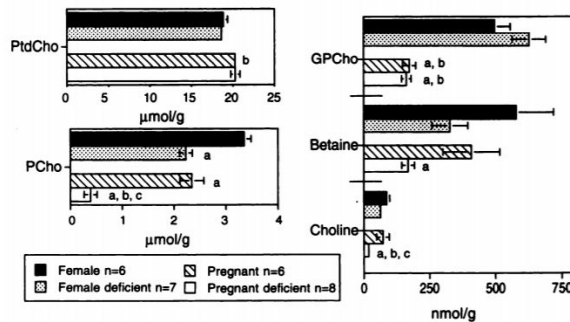
Choline & Aging - A Life Course Perspective



Targeting Aging: Why Choline & Pregnancy?

- Pregnancy is a critical window of exposure
 - Organ Development
 - Epigenetic programming
 - Stressed nutrient metabolism to facilitate maternal, fetal and placental requirements
- Choline in the amniotic fluid and fetal cord blood are several fold higher than in the maternal compartment
- In the rodent, maternal hepatic concentrations of choline metabolites are significantly diminished during pregnancy

Maternal Hepatic Metabolites, E18.5



Maternal Hepatic Metabolites, E20-22

Tissue	Source	Choline concentration (nmol/g)	
		Mean	s.e.m.
Liver	Non-pregnant adult	130	9.3
	Maternal	38	1.3
	Foetal	135	6.1
Placenta		442	17.9
Plasma	Non-pregnant adult	5.3	0.7
	Maternal	5.7	0.7

Choline in Pregnancy: A Key Developmental Period to Target Age-Related Cognitive Decline

Dose-Response Relationship

Supplementation (3-5x)
Promotes alterations in septohippocampal circuitry, improved long-term potentiation, and life-long improvements in visuospatial and auditory memory

03

Adequacy (AIN76/93 levels)
Maintains organ function without overt deficiency symptoms

02

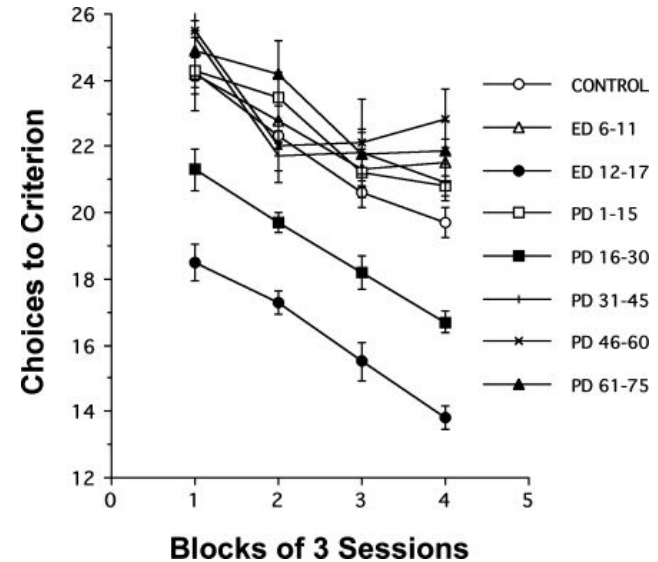
Deficiency (Choline-free)
Impairs offspring hippocampal development;
Worsened long-term potentiation & visuospatial and auditory memory

01



Maternal Choline Supplementation (MCS): Persistent Effects from a Critical Window

- In the rat, a gestational window between Embryonic Day 12-17 (E12-17) has consistently emerged as the critical window for MCS' effects
 - Known period of rapid hippocampal development
 - Corresponding to the late 1st trimester of human pregnancy through early postnatal life

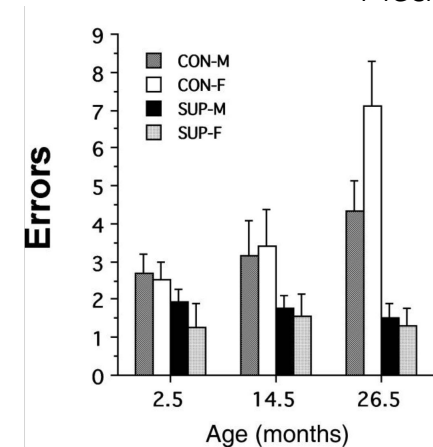
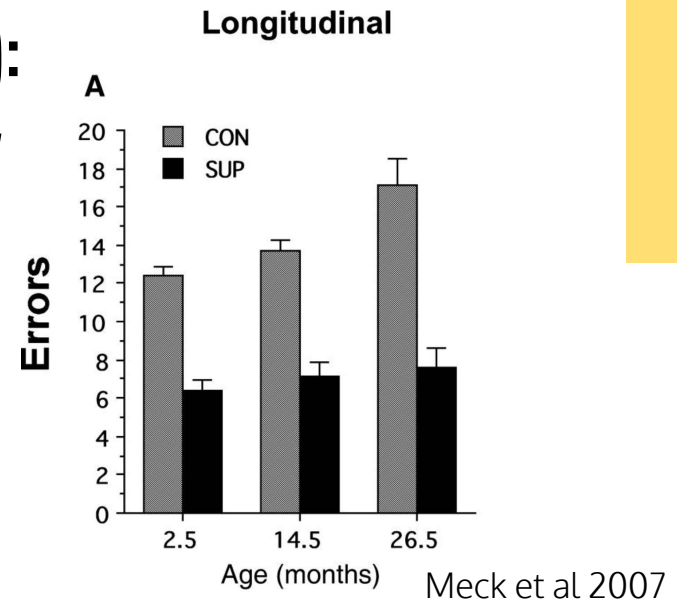


Adult (~7mo) 12 arm radial maze
training performance

Meck et al 2007

Maternal Choline Supplementation (MCS): Persistent Effects from a Critical Window

- Spatial memory training tests reveal a strong recalcitrance to age-related memory declines in E12-17 supplemented groups
 - Not fetal sex dependent
- MCS during E12-17 alters adult hippocampal morphology, including:
 - Dendritic spine density
 - Altered dentate granule cell morphology
- 1 example; MCS' effects have been repeatedly shown since the late 1980's across numerous investigators/labs across various behavioral domain tests

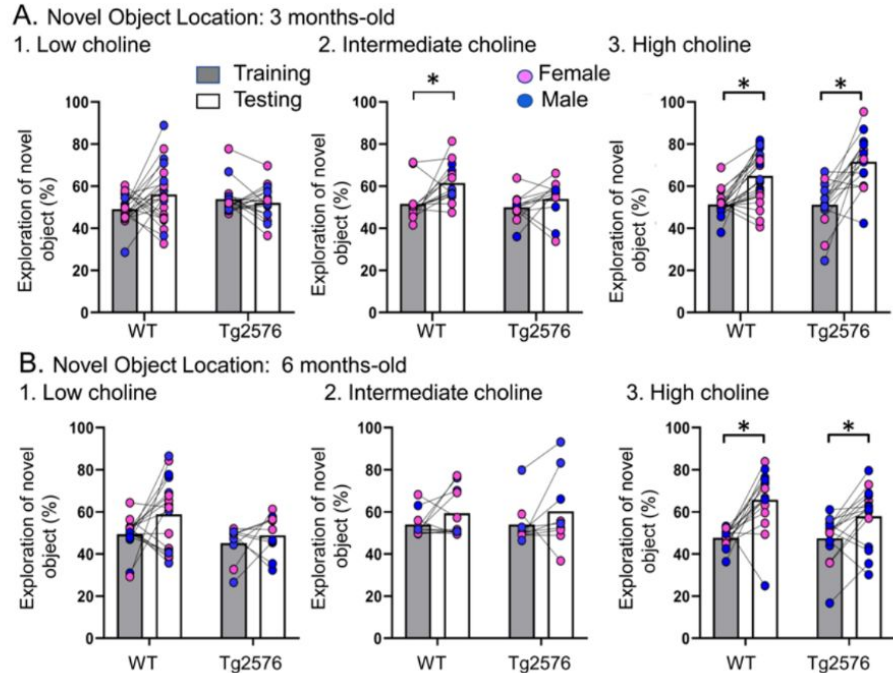


Choline supplementation in early life improves and low levels of choline can impair outcomes in a mouse model of Alzheimer's disease.

Elissavet Chartampila^{1,2}, Karim S. Elayouby^{1,3}, Paige Leary^{1,4}, John J. LaFrancois^{1,5}, David Alcantara-Gonzalez^{1,5}, Swati Jain¹, Kasey Gerencer^{1,6}, Justin J. Botterill^{1,7}, Stephen D. Ginsberg^{1,4,8,9}, and Helen E. Scharfman^{1,4,5,8,9}

bioRxiv

- Tg2576 mouse model of Alzheimer's Disease breeding pairs exposed to low-ish (1.1g/kg), intermediate (2g/kg), or high (5g/kg) choline diets until weaning (~30 days)
- Battery of various behavioral and histochemical outcomes



Mechanistic Insights?



Mechanistic Insights?

- Metabolic:
 - Choline at the high micromolar concentrations in utero is an efficient agonist for the $\alpha 7$ nicotinic receptor (Chrna7)
 - Brains of maternal choline supplemented fetuses exhibit high levels of betaine and phosphocholine
- Limited choline-x-transgenic animal investigations:
 - DBA/2 mice with a null mutation in Chrna7 (model of sensory inhibition defects schizophrenia) do not display the behavioral improvements from MCS (het-het breeding) where as wild-type control littermates do
- Some research suggests epigenetic effects of choline availability:
 - Defects in neurogenesis secondary to reduced EGFR signaling in neural progenitor cells and altered epigenetic state of cell cycle genes
 - Defects in hippocampal angiogenesis related to VEGF and ANGPT2 signaling and respective promoter methylation state



Does this translate to humans?

CAVEAT

- Do not currently have decade long RCT follow-up or strong prospective cohorts with 1) maternal choline intake exposure & 2) longitudinal neurobehavioral assessments
 - RCT cannot ethically study choline deficiency effects
 - Cohorts will fail to see MCS effects (given low rates of supplementation)
- As with all geroscience enthusiasm, the evidence-base in humans is a bit of a wet blanket

What evidence do we have?

Association between Maternal Choline, Fetal Brain Development, and Child Neurocognition: Systematic Review and Meta-Analysis of Human Studies

Rima Obeid,¹ Emma Derbyshire,² and Christiane Schön³

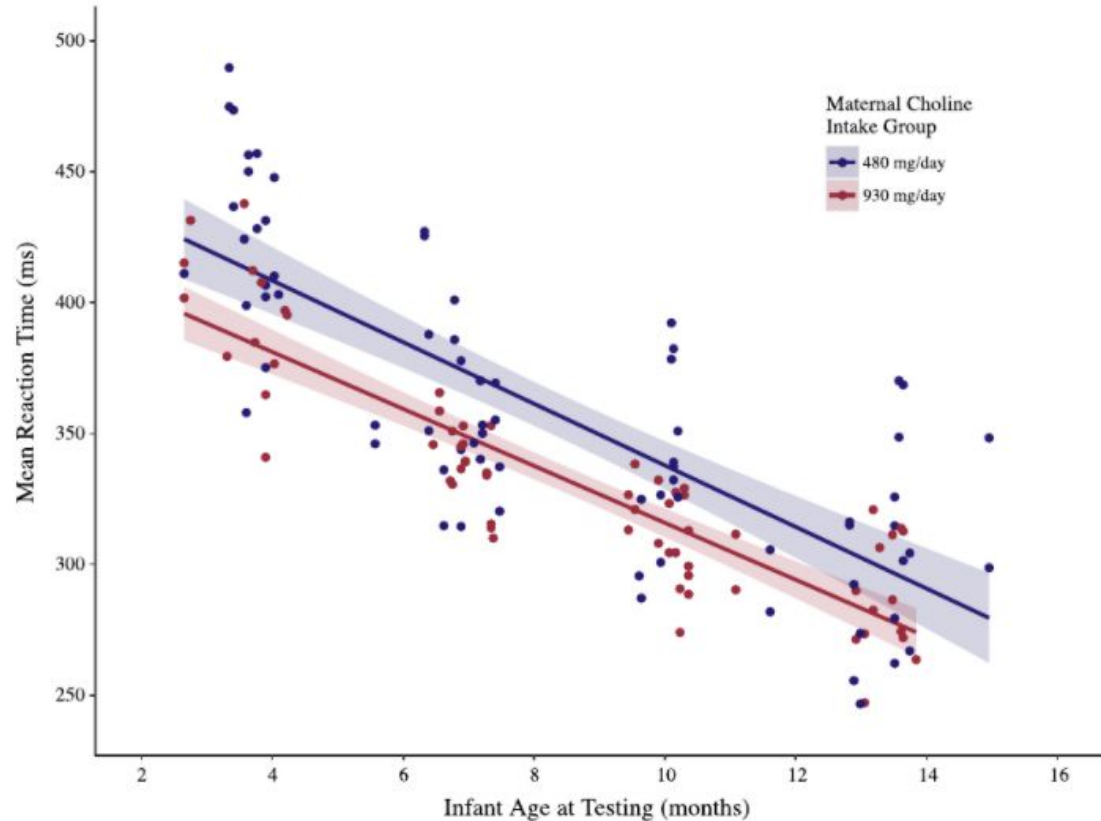
¹Department of Clinical Chemistry and Laboratory Medicine, University Hospital of the Saarland, Homburg, Germany; ²Nutritional Insight, Surrey, United Kingdom; and ³BioTeSys GmbH, Esslingen, Germany

- Randomized controlled trials of MCS
 - healthy pregnant people & alcohol-exposed pregnancies
 - 2nd-3rd trimester supplementation windows
 - Varied dosing (typically 2X+ background diet) and formulations (water vs lipid soluble)
 - Various cognitive outcomes
- Cohort Studies
 - Commonly 1-2 time points during pregnancy (diet assessment, plasma choline)
 - Infant/child cognition & behavior questionnaires, some functional testing
 - Adjustment for various diet, demographic and clinical/biochemical characteristics
- Heterogeneity in studies precludes meta-analysis

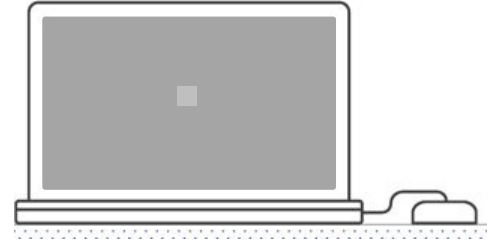
- 3rd Trimester Controlled Feeding study in healthy pregnant participants
- MCS improved the mean reaction time in visually guided reactive saccades
 - time for infants to detect peripheral stimulus and align fovea of the eye with the target

Maternal choline supplementation during the third trimester of pregnancy improves infant information processing speed: a randomized, double-blind, controlled feeding study

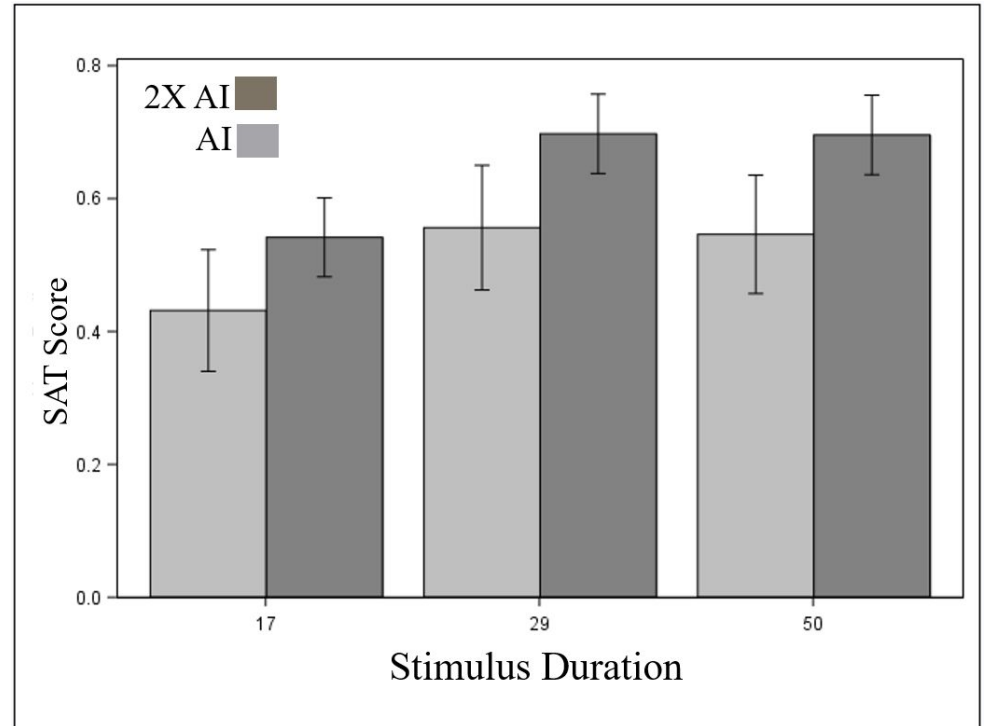
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MCS at 2X AI confers signal detection advantage



- Sustain Attention Testing (SAT) at 7 years of age
- SAT score combines detecting signals and rejecting non-signals
- Choline effect: $P=0.016$

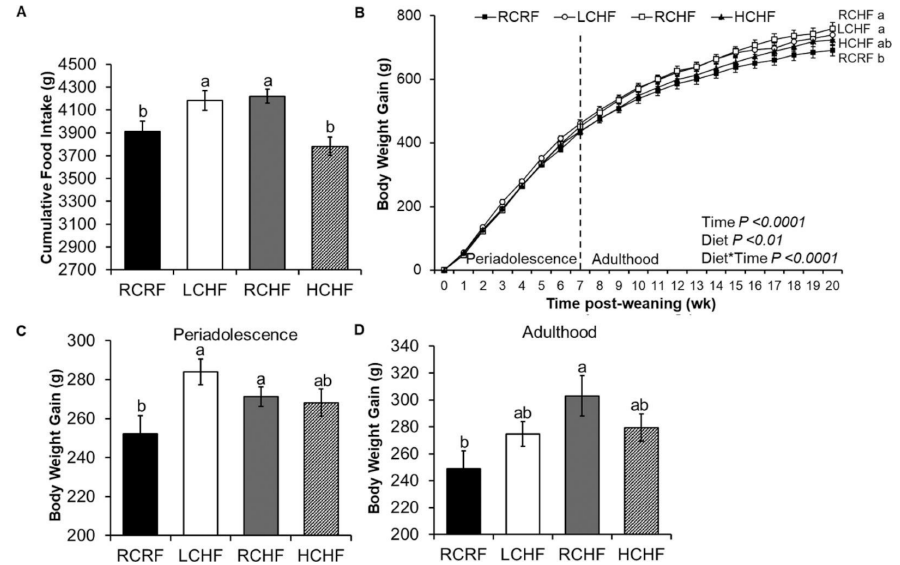


Summary:

- Critical gestational windows represent an opportunity to intervene with maternal choline supplementation to modify septohippocampal development and life-cycle neurocognitive aging
 - Exact mechanisms underlying these improvements are challenging to identify
 - To be improved by 1) diet-x-transgenic animal feeding studies; & 2) Single-cell RNA & Epigenetic techniques; 3) Histone Marks & Chromatin Topology (e.g. Hi-C)
- Translational to human studies is challenging:
 - Limited supplementation literature with choline salts supports persistent cognitive improvements in offspring exposed to MCS
 - Unclear relevance to other forms of choline supplements/dietary choline (PCs)
 - Need for stronger prospective cohort data with broad/precise life-cycle nutritional, metabolic and neurocognitive exposure/outcome data
 - Need for choline status indicator
 - Need to consider common genetic variants

Other Age-Related Phenotypes?

- MCS has been most well studied in the context of hippocampal development and offspring age-related cognition
- MCS is a part of nutrient cocktails that influence other phenotypes through epigenetic mechanisms:
 - Axin Fused (kinked tail) & Agouti loci (coat color)
 - Other phenotypes relevant to aging (e.g. muscle)? Epigenetic aging?
- Recent evidence using multifactorial diets demonstrate that high folic acid diet feeding during pregnancy can induce a hyperphagia & weight gain phenotype in the offspring that can be buffered by also feeding high choline





THANKS

Do you have any questions?
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