Scientific review of key references and citations
and
Cerebelly patent overview

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ANNOTATED BIBLIOGRAPHY WITH KEY REFERENCES:

SUMMARY OF THE CEREBELLY PATENT:

Biomechanical analysis of normal brain development during the first year of life using finite strain theory

Citation:

Kim, J. C., Wang, L., Shen, D., & Lin, W. (2016). Biomechanical Analysis of Normal Brain Development during the First Year of Life Using Finite Strain Theory. Scientific reports, 6, 37666.

Link to PubMed or available study:

https://www.ncbi.nlm.nih.gov/pubmed/27910866

Brief Summary:

This landmark study combined longitudinal MR imaging with finite strain theory to provide a nuanced view of normal brain development in the first year of life. 33 normal infants were imaged from 2 weeks to 1 year of age, every three months (a total of 5 MRIs per child). Size, rate and direction of growth are described for dozens of regions.

Sample Excerpts:

"The intracranial brain volume (ICV) increases by 101% in the first year and 15% in the second year, which is about 83% of the adult volume."

"Regions with prominent increase of JD are mainly in the right hemisphere adjacent to the interhemispheric fissure (cingulum, lingual, Fusiform, calcarine, cuneus, precuneus, rectus and olfactory gyri). Additionally, some areas of the visual cortex showed higher growth patterns (months 0–12). More importantly, regions related higher cognitive functions showed a higher volumetric growth from month 6 (temporal, parietal, angular and supramarginal gyri)."

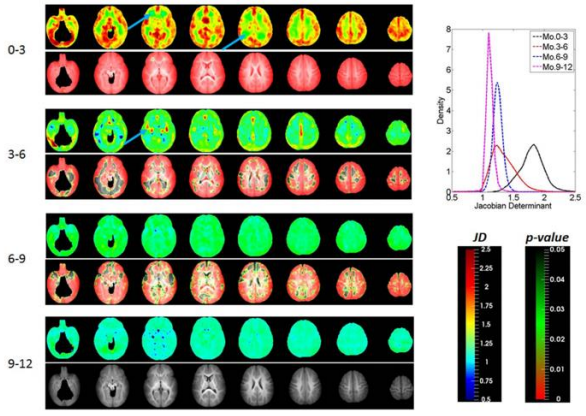

Figure 1. Mean volume growth rates (JD) of the four time periods during the first year of life. The anterior/posterior regions of corona radiate show the lowest local volume change during 0–3 months (arrows). A higher volume expansion at the insula cortex is observed during 3–6 months (arrow). Whole brain distributions of JD during the time periods are shown in the upper right column where x-axis and y-axis represent the JD values and the relative probability density, respectively.

Advocacy for improving nutrition in the first 1000 days to support childhood development and adult health

Citation:

Schwarzenberg, S. J., & Georgieff, M. K. (2018). Advocacy for improving nutrition in the first 1000 days to support childhood development and adult health. Pediatrics, 141(2), e20173716.

Link to PubMed or available study:

https://pediatrics.aappublications.org/content/141/2/e20173716

Brief Summary:

This policy statement from the Committee on Nutrition at the American Academy of Pediatrics outlines the importance of adequate macro- and micronutrient intake for infants and toddlers up to the age of 2 in establishing proper neurodevelopmental functions. Although it does not provide a comprehensive review of the data, it names key nutrients and brain processes and provides a strong rationale for providers to support healthy nutritional programs. It also directs the reader to important related policies and guidelines from medical and federal entities.

Sample Excerpts:

"...optimal, healthy neurobehavioral development requires that all necessary factors be present at their biologically defined time points..."

"Although all nutrients are necessary for brain growth, key nutrients that support neurodevelopment include protein; zinc; iron; choline; folate; iodine; vitamins A, D, B6, and B12; and long-chain polyunsaturated fatty acids. Failure to provide key nutrients during this critical period of brain development may result in lifelong deficits in brain function despite subsequent nutrient repletion. Understanding the complex interplay of micro- and macronutrients and neurodevelopment is key to moving beyond simply recommending a “good diet” to optimizing nutrient delivery for the developing child."

"The most active period of neurologic development occurs in the first 1000 days of life, the period beginning at conception and ending at the start of the third postnatal year."

Nutritional Influences on Brain Development

Citation:

Georgieff, M.K., Ramel, S.E., Cusik, S.E. (2017). Nutritional Influences on Brain Development. Acta Paediatrica ISSN 0803-5253.

Link to PubMed or available study:

https://www.ncbi.nlm.nih.gov/pubmed/29468731

Brief Summary:

Increasing evidence from preclinical and human studies show that early neonatal nutrition has a significant impact on neurodevelopment across the lifespan. This review from the Karolinska Institute in Sweden serves as a companion to the white paper above, "Advocacy for improving nutrition in the first 1000 days to support childhood development and adult health". It outlines, in a more extensive form, the principles of the nutrient-brain interaction, the specific nutrients required for healthy brain development, and the societal cost of malnutrition in early life.

Sample Excerpts:

"The neonatal brain in the human consumes 60% of the body's total oxygen and therefore caloric consumption. This truly remarkable value far exceeds that of nonhuman species including monkeys, sheep and rodents as well as that of the adult human. Rapidly growing organs are more vulnerable to damage if critical nutritional substrates that support that growth is not provided in adequate amounts."

"Another major principle is that the positive or negative effects of nutrients on the brain are based on the timing, dose and duration of the exposure. This principle resides biologically in the fact that the brain is not a homogenous organ. Rather, it is made up of distinct regions (e.g. hippocampus, cortex, striatum, cerebellum) and processes (e.g. myelination, neurotransmitters), each of which has a different developmental trajectory and set of nutrient requirements."

Nutrition and brain development in early life

Citation:

Prado, E. L., & Dewey, K. G. (2014). Nutrition and brain development in early life. Nutrition reviews, 72(4), 267-284.

Link to PubMed or available study:
https://www.ncbi.nlm.nih.gov/pubmed/24684384

Brief Summary:

This comprehensive review summarizes a large body of cellular and molecular evidence from animal studies linking nutrition to brain development, and provides a brief review of human studies looking at nutrient deficits in low/middle income countries. Neurodevelopment is a dynamic process that is highly influenced by experience. Adequate nutrition is one aspect of experience which the brain requires for normal development. Particular nutrients are required at particular times to support specific neurodevelopmental processes. The key nutrients required are: protein, glucose, essential fatty acids, iron, iodine, zinc, B vitamins, choline, and potentially copper. Infants and children who do not receive adequate nutrition are at risk of failing to reach their developmental potential in cognitive, motor, and social-emotional abilities.

Sample Excerpts:

"Nutrient deficiency is more likely to impair brain development if the deficiency occurs during a time period when the need for that nutrient for neurodevelopment is high. Various nutrients are necessary for specific neurodevelopmental processes. Each process occurs in different, overlapping time periods in different brain areas."

"Adequate nutrition is necessary for normal brain development. Nutrition is especially important during pregnancy and infancy, which are crucial periods for the formation of the brain, laying the foundation for the development of cognitive, motor, and socio-emotional skills throughout childhood and adulthood."

"Adequate nutrition can be considered an aspect of the environment that is expected by the brain for normal development."

"When a child is adequately nourished from conception through infancy, the essential energy, protein, fatty acids, and micronutrients necessary for brain development are available during this foundational period, establishing the basis for lifetime brain function. The well-nourished child is also better able to interact with his or her caregivers and environment in a way that provides the experiences necessary for optimal brain development."

In Brief: The science of early childhood development

Citation:

Prado, E. L., & Dewey, K. G. (2014). Nutrition and brain development in early life. Nutrition reviews, 72(4), 267-284.

Link to PubMed or available study:
https://developingchild.harvard.edu/resources/inbrief-science-of-ecd/

Brief Summary:

A brief introduction to the principles of neurodevelopment. The rate of brain development is highest in the first few months and years of life. Critical circuits are formed by a combination of genetic and environmental influences. Early life interventions to support proper brain development are likely to be more efficient than remediations in later life.

Sample Excerpts:

"Brains are built over time, from the bottom up. The basic architecture of the brain is constructed through an ongoing process that begins before birth and continues into adulthood. Early experiences affect the quality of that architecture by establishing either a sturdy or a fragile foundation for all of the learning, health and behavior that follow. In the first few years of life, more than 1 million new neural connections are formed every second."

A Structural MRI Study of Human Brain Development from Birth to 2 Years

Citation:

Knickmeyer, R.C., Gouttard, S., Kang, C., Evans, D., Wilber, K., Smith, J.K., Hamer, R.M., Lin, W., Gerig, G., Gllmore, J.H. (2008). A Structural MRI Study of Human Brain Development from Birth to 2 Years. J Neurosci 28(47): 12176-82.

Link to PubMed or available study:

https://www.ncbi.nlm.nih.gov/pubmed/19020011

Brief Summary:

This study uses longitudinal MRI to describe brain growth and development over the first two years of life, by imaging once per year from birth. They find that total brain volume by 2 years of age is 83% of adult volume. The volume of the cortical hemispheres increased by 88% in the first year and by 15% in the second year. The volume of the subcortical area (including brainstem) increased by 130% in the first year and by 14% in the second year. The cerebellum increased by a striking 240% from 2 weeks to 1 year, and increased by 15% from 1 to 2 years of age.

Sample Excerpts:

"Total brain volume increased 101% in the first year, with a 15% increase in the second. The majority of hemispheric growth was accounted for by gray matter, which increased 149% in the first year; hemispheric white matter volume increased by only 11%. Cerebellum volume increased 240% in the first year. Lateral ventricle volume increased 280% in the first year, with a small decrease in the second. The caudate increased 19% and the hippocampus 13% from age 1 to age 2. There was robust growth of the human brain in the first two years of life, driven mainly by gray matter growth. In contrast, white matter growth was much slower."

"TBV [Total Brain Volume] at 2–4 weeks of age is ~36% of adult volume; TBV at 1 year is ~72% of adult volume, and TBV at 2 years is ~83% of adult volume"

Nutrition and the developing brain: nutrient priorities and measurement

Citation:

Georgieff, M. K. (2007). Nutrition and the developing brain: nutrient priorities and measurement. The American journal of clinical nutrition, 85(2), 614S-620S.

Link to PubMed or available study:

https://www.ncbi.nlm.nih.gov/pubmed/17284765

Brief Summary:

This review discusses the specific nutrients required for healthy perinatal brain development, and summarizes the neurobehavioral assessments that are able to correlate nutrient deficits with neurologic dysfunction in human infants - including data generated by CAT, MRI, EEG, DTI, ABR, and ERP methods.

Sample Excerpts:

"Nutrients and growth factors regulate brain development during fetal and early postnatal life. The rapidly developing brain is more vulnerable to nutrient insufficiency yet also demonstrates its greatest degree of plasticity. Certain nutrients have greater effects on brain development than do others. These include protein, energy, certain fats, iron, zinc, copper, iodine, selenium, vitamin A, choline, and folate. The effect of any nutrient deficiency or overabundance on brain development will be governed by the principle of timing, dose, and duration."

"On balance, the brain's vulnerability to nutritional insults likely outweighs its plasticity, which explains why early nutritional insults result in brain dysfunction not only while the nutrient is in deficit, but also after repletion."

"Iron deficiency alters myelination, monoamine neurotransmitter synthesis, and hippocampal energy metabolism in the neonatal period."

"Zinc deficiency alters autonomic nervous system regulation and hippocampal and cerebellar development."

"Long-chain polyunsaturated fatty acids are important for synaptogenesis, membrane function, and, potentially, myelination."

The role of nutrition in cognitive development

Citation:

Fuglestad, A., Rao, R., Georgieff, M. K., & Code, M. M. (2008). The role of nutrition in cognitive development. Handbook in developmental cognitive neuroscience, 2, 623-641.

Link to publicly available study:

https://pdfs.semanticscholar.org/bce0/dff241628f3bb6388608303e54dbbf782ef0.pdf

Brief Summary:

This comprehensive book chapter 1) defines nutrient categories, 2) outlines the role of adequate nutrition in the context of cognitive development, and 3) elaborates on nutrient-specific neurodevelopmental deficits.

Sample Excerpts:

"Protein, fat, and carbohydrates are considered the three macronutrients. Minerals, trace elements, and vitamins are collectively grouped as micronutrients."

Pediatric Nutrition, Section IV Micronutrients

Citation:

Kleinman R.E., Greer, F.R. (2013). Pediatric Nutrition, 7th Edition. American Academy of Pediatrics.

Link to American Academy of Pediatrics eBook:

https://ebooks.aappublications.org/content/pediatric-nutrition-7th-edition?sso=1&sso_redirect_count=1&nfstatus=401&nftoken=00000000-0000-0000-0000-000000000000&nfstatusdescription=ERROR%3a+No+local+token

Brief Summary:

This AAP policy manual provides the latest information about nutrient metabolism to support the normal development and health of infants and children. Chapter IV of this reference focuses on the required micronutrients - and the physiological and health consequences of over or under abundance.

Sample Excerpts:

“Iron deficiency (ID) and iron deficiency anemia (IDA) continue to be of a worldwide concern. Among children in the developing world, iron is the most common single-nutrient deficiency. Even in industrialized countries, despite a demonstrable decline in prevalence, IDA remains a common cause of anemia in young children. Even more important is that even ID without anemia may adversely affect long-term neurodevelopment and behavior, and some of these effects may be irreversible.”

"zinc has also been shown to have a positive effect on physical activity of preschool children and on cognition and neurodevelopment"

"Uncorrected vitamin E deficiency during childhood leads to a progressive neurologic disorder"