King's Research Portal

DOI:

[10.1016/j.bbi.2018.07.009](https://doi.org/10.1016/j.bbi.2018.07.009)

Document Version

Peer reviewed version

[Link to publication record in King's Research Portal](#)

Citation for published version (APA):

Chang, J. P-C. (2018). More fish-happier mom, smarter child? *Brain, Behavior, and Immunity*.
<https://doi.org/10.1016/j.bbi.2018.07.009>

Citing this paper

Please note that where the full-text provided on King's Research Portal is the Author Accepted Manuscript or Post-Print version this may differ from the final Published version. If citing, it is advised that you check and use the publisher's definitive version for pagination, volume/issue, and date of publication details. And where the final published version is provided on the Research Portal, if citing you are again advised to check the publisher's website for any subsequent corrections.

General rights

Copyright and moral rights for the publications made accessible in the Research Portal are retained by the authors and/or other copyright owners and it is a condition of accessing publications that users recognize and abide by the legal requirements associated with these rights.

- Users may download and print one copy of any publication from the Research Portal for the purpose of private study or research.
- You may not further distribute the material or use it for any profit-making activity or commercial gain
- You may freely distribute the URL identifying the publication in the Research Portal

Take down policy

If you believe that this document breaches copyright please contact librarypure@kcl.ac.uk providing details, and we will remove access to the work immediately and investigate your claim.

“More Fish- Happier Mom, Smarter Child?”

Jane Pei-Chen Chang^{a,b,c*}

^aDepartment of Psychological Medicine, Institute of Psychiatry, Psychology and Neuroscience, King’s College London, London, UK

^bDepartment of Psychiatry, China Medical University Hospital, Taichung, Taiwan

^cCollege of Medicine, China Medical University, Taichung, Taiwan

* Correspondence concerning this article should be addressed to:

Dr. Jane Pei-Chen Chang

Institute of Psychiatry, Psychology & Neuroscience, King’s College London

G.33.68, The Maurice Wohl Clinical Neuroscience Institute

Cutcombe Road, London, SE5 9RT, United Kingdom

Telephone: 020 7848 0531

Fax: 020 7848 5408

Email: jane.chang@kcl.ac.uk

Childhood neurodevelopmental disorders have been attributed to several prenatal factors, including maternal diets (Madore et al., 2014) and maternal inflammation (Estes & McAllister, 2016; Patterson, 2009) during pregnancy. A report in this issue of *Brain, Behavior, and Immunity* used animal models to examine the protective effects of dietary omega-3 polyunsaturated fatty acids (n-3 PUFAs) during pregnancy on brain development of the offspring, in the context of environmental adversity such as maternal inflammation (Labrousse et al., 2018). Previous study showed that lower amount of maternal seafood intake, comprising of n-3 PUFAs, during pregnancy has been associated with suboptimal social developmental, fine motor, prosocial behavior and communication outcomes in the offspring (Hibbeln et al., 2007). Moreover, maternal n-3 PUFAs levels have been inversely associated with pro-inflammatory cytokine levels in women with perinatal depression (Chang, Lin, et al., 2018), and perinatal depression has been associated with poor developmental outcomes of the child (Kingston et al., 2018), and even increased the risk for depression as adults (Plant, Pariente, Sharp, & Pawlby, 2015). In addition, n-3 PUFAs deficiency has been associated with several neurodevelopmental disorders, including attention deficit hyperactivity disorder, autism and schizophrenia (Chang, Su, Mondelli, & Pariente, 2018; Maekawa et al., 2017; Mazahery et al., 2017). PUFAs are essential fatty acids with immunomodulatory properties (Calder, 2005) and can only be obtained from the diet. N-3 PUFAs, including docosahexaenoic acid (DHA) and eicosapentaenoic acid (EPA), favor anti-inflammatory responses, while omega-6 PUFAs promotes pro-inflammatory actions (Calder, 2006). However, the association between n-3 PUFAs deficiency, in the context of maternal inflammation during pregnancy, and the neurodevelopmental outcomes in the offspring still require further investigation. On the basis of human epidemiological findings, a number of translational rodent models have been established to help provide insight into such relationship by exploring the consequences of maternal immune activation (MIA) during

pregnancy on brain and behavioral development. In the current animal models of *in utero* inflammation, including MIA, pregnant animals are exposed to an immunological manipulation at a specific gestational stage. The immunological manipulation includes exposure to immunogens such as human influenza virus, the viral mimic- polyriboinosinic-polyribocytidilic acid, the bacterial endotoxin lipopolysaccharide (LPS), the locally acting inflammatory agent turpentine, or selected inflammatory cytokines. The MIA models are important in identifying the causal mechanisms that affect normal brain development in the event of early-life immune exposures. MIA has been associated with altered connectivity in the brain structures of neonates and toddlers (Spann, Monk, Scheinost, & Peterson, 2018), and has been suggested as a risk factor for neurodevelopmental disorders (Solek, Farooqi, Verly, Lim, & Ruthazer, 2018).

In this issue of *Brain, Behavior, and Immunity*, Labrousse et al. (2018) examined the effects of n-3 PUFAs dietary intake during pregnancy and lactation on the consequences of a LPS model of MIA on brain development. This is the first study to show n-3 PUFAs deficiency as a risk factor for the development of cognitive impairment in the offspring in the context of MIA. The present study is also the first to examine the effects of n-3 deficiency on the brain lipid composition and inflammation in MIA-exposed animals and their offspring. In the present study, the female mice had MIA triggered by the intraperitoneal administration of LPS at G17 (17 days after mating). The female mice were either fed n-3 deficient diet or n-3 balanced diet across gestation and lactation to modulate n-3/n-6 PUFAs in the offspring. The present study generated 4 cohorts of mice, cohort 1 was used for the assessment of memory performances, cohort 2 was used for the quantification of fatty acid levels and cytokines, cohort 3 was used for the Fluorescence-activated cell sorting (FACS) analysis, cohort 4 was used to assess the cFOS expression (or neuronal activation) and measure the fatty composition of adult livers and brainstems. The memory tests including the spatial

recognition and the novel object recognition were assessed at 3 months-old.

In the present study, n-3 PUFAs deficiency exacerbates the MIA-induced n-3 PUFAs-level decrease and increases the interleukin-6 (IL-6) production in maternal blood, placenta and fetal brain. Moreover, IL-6 production and DHA levels are anti-correlated in the fetal brain, while DHA affects the brain in a region-specific manner, particularly the hippocampus. In addition, n-3 deficiency has been associated with decreased neuronal activation in the dentate gyrus of the MIA-exposed animals, and hippocampal-dependent spatial memory deficits in the adult offspring.

The findings of the present study may help shed some light on the answer to the question of whether mandatory dosages of n-3 PUFAs supplementation for mothers during pregnancy should be implemented. The present study not only addresses the importance of deleterious effects of maternal n-3 PUFAs deficiency on the brain development of the offspring in the context of MIA, but further supports the action of n-3 PUFAs on cognitive function may be via modulation of cytokine production without affecting microglial phenotype. Clinical study showed that mothers with prenatal depression have a higher level of inflammation and a lower level of n-3 PUFAs than mothers without perinatal depression (Chang, Lin, et al., 2018), and n-3 PUFAs supplementation has been shown to improve prenatal depression (Su et al., 2008). The present study further emphasized the importance of having ‘enough’ n-3 PUFAs during pregnancy in mothers who are prone to immune activation, including perinatal depression. Of note, perinatal period is a critical window for n-3 PUFAs on brain development, where the build-up of n-3 PUFAs during this period will significantly affect later cellular and behavioral activities, especially when there are other environmental adversities.

Conflict of Interest

None

Acknowledgments

Dr. Chang is supported by the following grants: 104-2314-B-039-050-MY3, 103-2320-B-039-036, from Ministry of Science and Technology, Taiwan.

Reference

- Calder, P. C. (2005). Polyunsaturated fatty acids and inflammation. *Biochem Soc Trans*, 33(Pt 2), 423-427. doi:10.1042/BST0330423
- Calder, P. C. (2006). n-3 polyunsaturated fatty acids, inflammation, and inflammatory diseases. *Am J Clin Nutr*, 83(6 Suppl), 1505S-1519S. doi:10.1093/ajcn/83.6.1505S
- Chang, J. P., Lin, C. Y., Lin, P. Y., Shih, Y. H., Chiu, T. H., Ho, M., . . . Su, K. P. (2018). Polyunsaturated fatty acids and inflammatory markers in major depressive episodes during pregnancy. *Prog Neuropsychopharmacol Biol Psychiatry*, 80(Pt C), 273-278. doi:10.1016/j.pnpbp.2017.05.008
- Chang, J. P., Su, K. P., Mondelli, V., & Pariante, C. M. (2018). Omega-3 Polyunsaturated Fatty Acids in Youths with Attention Deficit Hyperactivity Disorder: a Systematic Review and Meta-Analysis of Clinical Trials and Biological Studies. *Neuropsychopharmacology*, 43(3), 534-545. doi:10.1038/npp.2017.160
- Estes, M. L., & McAllister, A. K. (2016). Maternal immune activation: Implications for neuropsychiatric disorders. *Science*, 353(6301), 772-777. doi:10.1126/science.aag3194
- Hibbeln, J. R., Davis, J. M., Steer, C., Emmett, P., Rogers, I., Williams, C., & Golding, J. (2007). Maternal seafood consumption in pregnancy and neurodevelopmental outcomes in childhood (ALSPAC study): an observational cohort study. *Lancet*, 369(9561), 578-585. doi:10.1016/S0140-6736(07)60277-3
- Kingston, D., Kehler, H., Austin, M. P., Mughal, M. K., Wajid, A., Vermeyden, L., . . . Giallo, R. (2018). Trajectories of maternal depressive symptoms during pregnancy and the first 12 months postpartum and child externalizing and internalizing behavior at three years. *PLoS One*, 13(4), e0195365. doi:10.1371/journal.pone.0195365
- Labrousse, V. F., Leyrolle, Q., Amadiou, C., Aubert, A., Sere, A., Coutureau, E., . . . Laye, S. (2018). Dietary omega-3 deficiency exacerbates inflammation and reveals spatial memory deficits in mice exposed to lipopolysaccharide during gestation. *Brain Behav Immun*. doi:10.1016/j.bbi.2018.06.004
- Madore, C., Nadjjar, A., Delpech, J. C., Sere, A., Aubert, A., Portal, C., . . . Laye, S. (2014). Nutritional n-3 PUFAs deficiency during perinatal periods alters brain innate immune system and neuronal plasticity-associated genes. *Brain Behav Immun*, 41, 22-31. doi:10.1016/j.bbi.2014.03.021
- Maekawa, M., Watanabe, A., Iwayama, Y., Kimura, T., Hamazaki, K., Balan, S., . . . Yoshikawa, T. (2017). Polyunsaturated fatty acid deficiency during neurodevelopment in mice models the prodromal state of schizophrenia through epigenetic changes in nuclear receptor genes. *Transl Psychiatry*, 7(9), e1229. doi:10.1038/tp.2017.182
- Mazahery, H., Stonehouse, W., Delshad, M., Kruger, M. C., Conlon, C. A., Beck, K. L., & von Hurst, P. R. (2017). Relationship between Long Chain n-3 Polyunsaturated Fatty Acids and Autism Spectrum Disorder: Systematic Review and Meta-Analysis of Case-Control and Randomised Controlled Trials. *Nutrients*, 9(2). doi:10.3390/nu9020155
- Patterson, P. H. (2009). Immune involvement in schizophrenia and autism: etiology, pathology and animal models. *Behav Brain Res*, 204(2), 313-321. doi:10.1016/j.bbr.2008.12.016
- Plant, D. T., Pariante, C. M., Sharp, D., & Pawlby, S. (2015). Maternal depression during pregnancy and offspring depression in adulthood: role of child maltreatment. *Br J Psychiatry*, 207(3), 213-220. doi:10.1192/bjp.bp.114.156620
- Solek, C. M., Farooqi, N., Verly, M., Lim, T. K., & Ruthazer, E. S. (2018). Maternal immune activation in neurodevelopmental disorders. *Dev Dyn*, 247(4), 588-619.

doi:10.1002/dvdy.24612

- Spann, M. N., Monk, C., Scheinost, D., & Peterson, B. S. (2018). Maternal Immune Activation During the Third Trimester Is Associated with Neonatal Functional Connectivity of the Salience Network and Fetal to Toddler Behavior. *J Neurosci*, 38(11), 2877-2886. doi:10.1523/JNEUROSCI.2272-17.2018
- Su, K. P., Huang, S. Y., Chiu, T. H., Huang, K. C., Huang, C. L., Chang, H. C., & Pariante, C. M. (2008). Omega-3 fatty acids for major depressive disorder during pregnancy: results from a randomized, double-blind, placebo-controlled trial. *J Clin Psychiatry*, 69(4), 644-651.