

Format for ANSWERING REVIEWERS

January 12, 2015



Dr. Editor,

Please find enclosed the edited manuscript in Word format (file name: 13521-review.doc).

Title: Role of Perinatal Long-Chain Omega-3 Fatty Acids in Cortical Circuit Maturation: Mechanisms and Implications for Psychopathology

Author: Robert K McNamara, Jennifer J Vannest, Christina J Valentine

Name of Journal: *World Journal of Psychiatry*

ESPS Manuscript NO: 13521

The manuscript has been improved according to the suggestions of reviewers:

Reviewer #1:

"This is an interesting paper, with an important contribution to understanding neurobiology. I suggest

the review to be accepted in the World Journal of Psychiatry."

Reviewer #2:

1) *"Some inferences are insufficient. For example, the authors addressed the association of longer duration of breastfeeding and attention/executive function. It may be just one of many risk factors for*

ADHD. Except longer duration of breastfeeding do not absolutely associate with and infants receiving

DHA, it is more important that longer duration of breastfeeding may bring other effects on infants, such

as a better mother-child attachment relationship. Compare to DHA, attachment relationship may play

more critical role for mental illness.” Response: We agree that longer breastfeeding duration may

have beneficial effects on neurodevelopment that are not mediated DHA, and now state:

“However, the

latter studies did not determine breast milk DHA concentrations to evaluate contribution to functional

outcomes and additional/alternative benefits of longer breastfeeding (i.e., better mother-child attachment) may also play an important role.”

2) *“The causal relationship between impaired cortical circuit connectivity and ADHD and other psychotic disorders as the authors mentioned is still unclear now. Some evidence indicates that there*

is a correlation between them, but it does not mean that there is a causal relationship. DHA may explain the appearance of impaired cortical circuit connectivity, but DHA or impaired cortical circuit

connectivity also must be able to explain other symptoms of these disorders. Otherwise, there are a lot

of risk factors may contribute to these possible etiology of ADHD and mood and psychotic disorders.

When we say that DHA play ‘critical’ role on them, there must be more certain evidence to show its unique contribution.” Response: We agree and have tempered our conclusions regarding

these

associations. Specifically, we have removed the term ‘critical’ when referring to the role of DHA in

cortical circuit deficits in psychiatric disorders. We also now state: “Although the initial onset of major

psychiatric disorders commonly coincides with active and dynamic changes in frontal circuit connectivity, and psychopathology is associated with deficits in frontal circuit connectivity, a causal

relationship has not been established.”

3) *"The authors attempted to do a big conclusion by insufficient evidences in DHA for human neurodevelopment. There are still many details should be clarify. The conclusion should be more cautious."* **Response:** We agree and where appropriate have used terminology including "...additional research is needed...", "...these findings support the hypothesis...", "...these associations suggest...", "...may play a role...", "...additional studies will be required to evaluate..." and "...It is not currently known..." to indicate that the discussed relationships are tentative pending additional evidence.

4) *"Since the paper is focus on the psychiatric disorder of human, I suggested the text on the mechanism could be trimmed, and focused on the human studies. The text about animal models could be shorten and adjusted to the beginning."* **Response:** The main focus of this paper is on the role of omega-3 fatty acids (DHA) in cortical circuit maturation, and we explore implications for psychiatric disorders. We therefore feel that review of animal studies, which provide more definitive evidence for such a role, be included to set the stage for discussions regarding relevance to psychiatric disorders which is currently more controversial.

5) *"A very brief description on the evidence supporting the role of DHA on each psychiatric disorder mentioned in this paper could be added on end of P. 11."* **Response:** On pages 12-14, we do discuss extant evidence from cross-national and cross-sectional epidemiological surveys, case-control peripheral and central studies (and associated meta-analyses), and omega-3 supplementation trials (and associated meta-analyses) implicating DHA in each psychiatric disorder.

6) "A paragraph (or a box) as a concise summary on the mechanisms before the section "Implications for psychopathology" might be beneficial for readers from clinical practice." **Response:** We agree and have added the following summary paragraph: *"In summary, evidence from animal studies suggests that normal brain development requires optimal levels of DHA which has neurotrophic and neuroprotective properties. A potential ultrastructural mechanism mediating the beneficial effects of DHA on synaptic maturation and axodendritic connectivity is increased F-actin cytoskeletal stability in pre- and post-synaptic terminals mediated through reductions in PKC activity. Additional evidence from non-human primate and clinical imaging studies suggest that low DHA levels during perinatal development may lead to long-standing impairments in functional connectivity in cortical networks as well as the emergence of cognitive impairment, hyperactivity/inattention and emotional symptoms in children. Taken collectively, these associations support the assertion that cortical DHA accrual during perinatal brain development may play a role in the maturation of human cortical networks mediating cognitive and emotional processes."*

We thank the reviewers for their constructive comments, and hope that this revised manuscript in now suitable for publication as a Review article in *World Journal of Psychiatry*.

A handwritten signature in black ink, appearing to read "R K McNamara". The signature is fluid and cursive, with the first letters of the first and last names being capitalized and prominent.

Sincerely,

Robert K. McNamara, Ph.D.

Associate Professor of Psychiatry