From homicide to happiness--a commentary on omega-3 fatty acids in human society. Cleave Award Lecture

Article *in* Nutrition and health (Berkhamsted, Hertfordshire) · February 2007

DOI: 10.1177/026010600701900204 · Source: PubMed

CITATIONS
16

READS
66

1 author:

Joseph R Hibbeln
National Institutes of Health
223 PUBLICATIONS **11,066** CITATIONS

SEE PROFILE

Nutrition and Health, 2007, Vol. 19, pp. 9–19
0260-1060/06 $10

FROM HOMICIDE TO HAPPINESS – A Commentary on Omega-3 Fatty Acids in Human Society

JOSEPH R. HIBBELN – CLEAVE AWARD LECTURE

Section on Nutritional Neurosciences, Laboratory of Membrane Biochemistry and Biophysics, National Institute on Alcohol Abuse and Alcoholism

ABSTRACT

The field of omega-3 fatty acid deficiencies as reversible risk factors in major psychiatric disorders has flourished in the last decade. Treatment recommendations of the American Psychiatric Association may be considered for application to more normative states of psychiatric health. Considered here is the proposition that an increased risk of personality disorders, and an increased sense of despair in normative populations, might be considered as symptoms of deficiencies of omega-3 fatty acids. The major changes in the essential fatty acid composition of the food supply, including increased availability of the omega-6 linoleic acid, may be correlated not only with increased risks of homicide, but also increased risks of suicide and suboptimal social cohesion.

Key words: Omega-3 fatty acids, polyunsaturated, homicide, aggression suicide, major depression, seed oils, linoleic acid, soy oil.

OVERVIEW

More than a decade of clinical and basic research has been conducted since publication of our hypothesis (Hibbeln and Salem, 1995) that deficiencies in omega-3 fatty acid intakes may increase risk of depression and affective disorders and that dietary replenishment may have treatment efficacy in depression, aggression and stress reduction. The McCarrison Society has very kindly acknowledged my work with the T.L. Cleave award and has provided, in this invited paper, an opportunity to reflect upon progress in selected themes outlined in that hypothesis paper.

Author for correspondence: CDR Joseph R. Hibbeln MD, National Institute on Alcohol Abuse and Alcoholism, 31 Center Drive 1B58 MSC 2088, Bethesda, MD 20892-2088, P: (301) 435-4028 F:(301) 402-0016, jhibbeln@mail.nih.gov

Thus, this manuscript is not intended so much as a critical examination of the field, but as a comment of the broad directions and societal implications of this flourishing field of research. One landmark however is the accumulation of substantial enough evidence for the American Psychiatric Association to issue treatment recommendations for patients with most psychiatric illnesses to consume at least 1 g of eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) per day or eat 3 fish meals per week (Freeman *et al*., 2006b). This treatment recommendation was based in part on the results of a meta-analysis of randomized placebo controlled trials in depression.

This meta-analysis of 9 randomized trials found a large treatment effect size of g = 0.54, which is a greater treatment effect size for reducing depressive symptoms than most antidepressants. Thus, the field has progressed from hypothesis to first treatment recommendations in 11 years. Still, because of the relatively low numbers of total subjects studied in major depression as well as other affective disorders, the absence of a large well conducted multi-centre trial, and uncertainties of the relative contributing roles of EPA and DHA, substantial work remains to be done. Unknown clinical questions include characterization of subjects likely to respond, and what neuropsychiatric symptoms might improve for those with diagnosable pathological conditions, and for those people with distress that is considered normative.

NEW DEFINITIONS OF SYMPTOMS OF DEFICIENCIES OF EPA AND DHA?

Preventing nutritional deficiencies and mental ill health?

Omega-3 fatty acids differ substantially from pharmacological treatments as they may more generally support the health of neurological tissues by optimizing multiple interacting signal transduction, neurotransmitter neurohormonal and gene transmission mechanisms that regulate the generation of new synapses (Sinclair *et al*., 2007). The concept that the manifestation of depressive and aggressive symptoms may result from a nutritional deficiency of EPA and DHA is critically different conceptualization from traditional pharmacological and psychotherapeutic approaches to treating depression, aggression and other psychiatric disorders. Most critically, the burden of attributable illness and approaches to prevention can be reformulated. This has made possible estimation of the prevalence of depressive illnesses attributable to nutritional deficiency, conceptually opening the possibility of attempting primary and secondary prevention trials as has been done with cardiovascular diseases. Nearly every other field of medicine actively considers and funds research towards understanding nutritional excesses and deficiencies as contributing risk or protective factors for illnesses. The series of ecological and epidemiological studies that uniformly find

that low seafood consumption correlates with up to 65-fold greater rates of depressive illnesses, and greater risks of anger and aggressive behaviour (Hibbeln, 1998; Hibbeln, 2001; Hibbeln, 2002; Hibbeln *et al*., 2007; Hibbeln *et al*., 2006; Tanskanen *et al*., 2001a; Tanskanen *et al*. 2001b), have never been presented as causal tests of efficacy. These studies do serve as more than pilot data and justification for intervention trials: these studies indicate the potential magnitude of improvements in the mental health of modern societies that might be accrued by eliminating deficient intakes of these essential nutrients.

THE SPECTRUM OF FEELINGS

The spectrum of emotional states affected by omega-3 fatty acids may span from the deepest existential despair and suicide to the most delightful, delicate and sublime poetic expression of spiritual happiness. Data already exists indicates that while nutritional deficiencies of EPA and DHA appear to increase risk of emotional distress, impulsivity and rage resulting in homicidal and suicidal behaviour, "sufficiency" of intake may need to be defined as happiness. Happiness, as a neurologically mediated emotional state, has not much been considered as an endpoint measuring nutritional sufficiency. This perspective is supported by the placebo controlled intervention trial of subjects with deliberate self-harm such as cutting or overdose (Hallahan *et al*., 2007) which found that 2 gm/d not only reduced suicidal thinking, symptoms of major depression and self perception of stress, the intervention also elevated perceptions of happiness on the Daily Hassles and Uplifts scale. Borderline personality disorder is characterized by volatile interpersonal relationships, fragile sensitivity to perceived insults and frequent outbursts of anger. When women with this personality disorder received 1 gm/d of ethyl ester EPA, verbal outbursts were reduced by 75% (Zanarini and Frankenburg, 2003). It is reasonable to assume that interpersonal relationships would become less volatile. Among a normal community sample of 200 subjects, lower plasma levels of DHA and EPA correlated with greater personality traits of neuroticism, while greater DHA correlated with greater agreeableness and cognitive impulsivity (Conklin *et al*., 2007). Decreased omega-3 status has been reported among paedophiles (Maes *et al*., 2005)and subjects with chronic fatigue syndrome (Mincke *et al*., 2006). These findings remained significant after adjustment for confounding variables in multivariate analyses. Among healthy Japanese students, supplementation with omega-3 fatty acids reduced anger measures and reduced plasma catecholamines (Hamazaki *et al*., 1996; Hamazaki *et al*., 1999). Supplementation reduced anger measures among elderly Thai subjects (Thienprasert *et al*., 2000). Together, these findings suggest that greater omega-3 fatty acid status is associated with better in affect regulation, personality and impulse control in normative non-pathological populations. It is reasonable to pose the question of a new

possible conceptualization of sufficiency of nutritional intake of EPA and DHA: is sufficiency an absence of pathology or an optimization of personal and societal happiness?

Social bonding and omega-3 fatty acids?

A broader question is to what depth might our societal happiness or sense of collective meaning be impaired by deficiencies in omega-3 fatty acids? One approach to examining that question has been an evaluation of the meaning of fish as a cultural symbol (Reis and Hibbeln, 2006). The data from randomized studies in major depression, suicide and aggression indicate that fish is a food with psychotropic properties because it is rich in long chain omega-3 fatty acids that improve mental well-being that is, change emotional states. Central to the neuroscience of the assignment of meaning to a visual object is the pairing of that object to an emotional state. Symbols of foods or other substances with psychotropic properties may become paired to the emotional states the substances induce. It is our hypothesis that traditional cultural medical practices and religious symbolism reflect the ability of long chain omega-3 fatty acids in fish and seafood to moderate aggressive, impulsive, and violent behavior. Symbols of fish may have become consciously and unconsciously associated with the healing of mental illness and the optimization of emotional well-being sacred to both religion and healing. Throughout time, religious and spiritual practitioners have altered their dietary practices, observed their altered internal states, and linked dietary practices to spiritual beliefs using religious and cultural symbols. Food appears to be the most ancient medicine for physical and mental health. In traditional Chinese medicine, seafood is used to calm excessive aggression. In Hinduism, Buddhism, Shinto, Islam, ancient Middle Eastern religions, Judaism, and Christianity, fish is symbolically associated with central tenets of faith and healing. For at least six millennia among independent cultures, fish has nearly universally been symbolically associated with sacred symbols of peace and religion.

The physiological and psychological value of fish?

My co-author and I have proposed that the associative pairing of emotions to symbols has linked the psychotropic properties of long chain omega-3s to core cultural paradigms of purity and health (Reis and Hibbeln, 2006). Throughout time, mental ill health (by which we mean to include not only mental illness that meets diagnostic criteria, but also sub-optimal mental health) has been associated with impurity, personal, cultural, and spiritual disruption, while optimal mental health has been associated with purity, cultural cohesion, and spiritual and internal harmony. We noted that the

healing properties of foods have nearly always had a spiritual or religious context, and that eating foods with healing properties serves to reintegrate the mentally ill back into spiritual harmony. Furthermore, one of the most common ways for an individual to reaffirm his or her cultural identity is to consume "pure" or sacred foods, both in the context of ceremony and in everyday life. The phrase "you are what you eat" has not only a biochemical interpretation, but also reflects food selection as a definition of cultural and personal identity.

Because seafood is a uniquely rich source of these psychoactive molecules, it is reasonable to expect that, over the course of human history, the emotional states induced by long chain omega-3s would have become associatively paired with symbols of fish and seafood. The phenomenonology of the pairing of emotions to stimuli is well described by theories of classical and operant conditioning; (Skinner, 1938). Pavlov demonstrated that a meaningless stimulus can become associated with a physiological, emotional, or behavioral state such as hunger through simple conditioned response, and the association is not necessarily consciously perceived (Pavlov, 1951). Objects visually perceived by the occipital cortex have no inherent meaning until they become associated with emotional valence and historical or cultural context; only when pairing occurs does an object have emotional, cultural, or historical meaning (Damasio, 1994). The necessity of emotion to meaning is demonstrated by the functional interdependence of the amygdala, a region of the brain essential to emotions such as fear, and the hippocampus, a region of the brain essential to the formation of new memories, as well as other brain regions (Dolan, 2002).

Contradictions between advice and evidence

It is interesting that fish has become labelled as polluted and in a sense symbolically transformed into an impure food by the 2004 US EPA and FDA advisory that women of childbearing potential should limit fish consumption during pregnancy due to concerns over potential neurotoxicity resulting from exposures to trace amounts of methyl-mercury. Since this advisory did not quantitatively assess the risks of harm from potential deficiencies resulting from inadequate intakes of nutrients rich in seafood, we assessed the efficacy of the advisory among 11,875 women and infant pairs participating in the Avon Longitudinal Study of Parents and Children (Hibbeln *et al*., 2007). We found that consumption concordant with the limits advised, at or below 340 gm/week, was associated with an increased risk of the detrimental effects the advisory intended to prevent. Specifically, there was in increased risk of children with suboptimal verbal IQ, fine motor development, communications development, social development at age 3 and impaired prosocial development at age 7. As inadequate fish intake increased risk of suboptimal social development scores for individual children, these findings are consistent with

the proposition that on a societal or population level, inadequate seafood intake may increase the risk for poor social cohesion.

Deficient dietary intakes of omega-3 fatty acids may not only impair optimal neurological development of the foetus, deficiencies may harm the mother during pregnancy. An ecological study found that the risk of postnatal depression was 50-fold greater in countries with little seafood consumption, compared to those with the highest consumption (Hibbeln, 2002). The incidence of postnatal depression is also inversely correlated with concentrations of docosahexaenoic acid (DHA) in plasma (Otto et al 2003) and breast milk (Hibbeln, 2002). Women with postnatal depressive symptoms have been shown to have several indicators of neural DHA deficiency (Otto *et al*., 2003). The proposition that deficiencies of EPA and DHA increase the risk of other affective illnesses, including major depression (Hibbeln 2002), bipolar disorder (Noaghiul and Hibbeln, 2003), anger (Iribarren *et al*., 2004) and homicide (Hibbeln, 2001)is supported by epidemiological and ecological studies. Open trials of EPA and DHA report 50% reductions of depressive symptoms both during and after pregnancy (Freeman *et al*., 2006a). Multiparity is associated with an increased risk for depression in pregnancy and postnatally, although this is usually interpreted as an association with the number of children in the household. In animal models, multiparity causes progressive depletion of DHA in maternal brains when dietary intakes are limited (Levant *et al*., 2006a; Levant *et al*., 2007; Levant *et al*., 2006b). It would be a shame if inadequate dietary intakes of omega-3 fatty acids change the emotional experience of pregnancy and child birth from happiness to depression and despair. If so, perhaps these deficiencies may be adversely altering the very meaning of motherhood and childbirth by altering the emotions attached to this experience.

Dietary trends and evaluation methodology

We (Hibbeln and Salem, 1995; Crawford *et al*., 2005) and others have proposed that the divergence of essential fatty acid intakes from evolutionary compositions to the compositions of modern industrialized societies has significantly contributed to increased risks of major psychiatric disorders. While this is an attractive proposition, there are significant methodological difficulties in evaluating this hypothesis for changes in diet in any country and for changes in any psychiatric disorder or behavioural condition. First has been obtaining data of any kind on dietary intakes at multiple time points in a single country. In general, most countries have few community based surveys of dietary intakes such as the United States NHANES study. Second is that the survey methods change at every iteration and there are few year by year assessments. Evaluation of community sample studies of the prevalence of psychiatric disorders is even more problematic as they are relatively few in number and have been generally conducted only in the last quarter of the

20th century. Dietary data that are available on a year by year basis are the apparent consumption or disappearance of foods, obtained from commodities databases. While not direct dietary survey data, and given multiple caveats such as assumptions of uniform wastage and home production, these data do nonetheless allow for the examination of trend changes for whole countries over time. As for the assessment of psychiatric disease, we have utilized data on homicide mortality since the diagnosis is consistent over time, the data is prospectively collected, and national data, not relying on a sub-sample does, like the commodities data, reflect trend changes for nations as a whole. With these caveats in mind, we have previously reported that increases in the apparent consumption of linoleic acid (18:2n-6) from seed oils closely correlated with increased rates of homicide mortality from 1961–2000 in 5 Western countries with "industrialized" (or modern) food supplies (Hibbeln *et al*., 2004). Greater dietary intakes of omega-6 fatty decrease tissue compositions of EPA and DHA (Hibbeln *et al*., 2006; Holman, 1998). If the extreme endpoints of behavioural pathology e.g. homicide and suicide are increased by these dietary changes, then what might be the changes to the more difficult to quantify disruptions in the fabric of social cohesion? Clearly changes in the essential fatty acids cannot be a sole factor contributing to the adverse social conditions currently existing, but what if some portion of the adverse social disruptions are attributable to specific nutritional deficiencies which can potentially be corrected?

EPA and DHA and serotonergic function

One important conceptual thread central to the neurobiology of depression homicide and suicide, which has not yet been adequately tested, is the proposition that inadequate EPA and DHA intakes reduce serotonergic function, either by reductions in numbers of functional neurons or synapses, or by decreased metabolism of serotonin. Reductions in serotonergic function or markers of serotonin levels, such as 5-hydroyindolacetic acid (5-HIAA), have been repeatedly linked to impulsive behaviours including self-harm, suicide and aggression (Mann *et al*., 1999). We are aware of little direct data in humans, but have reported that low concentrations of DHA in plasma of healthy volunteers and late onset alcoholics are correlated with lower levels of 5-HIAA in cerebrospinal fluid (Hibbeln *et al*., 1998). The most robust animal data consistent with this hypothesis is in piglets. For 18 days after birth, animals were fed standard infant formulas which contained no DHA or AA, and compared to animals feed formulas containing low levels of DHA and AA (de la Presa Owens and Innis, 1999). In the frontal cortex, levels of serotonin, 5-HIAAA, dopamine and its metabolite homovanillic acid were nearly doubled (de la Presa Owens and Innis, 1999). Strikingly, while large reductions in dopamine concentrations and release due to diets deficient in omega-3 fatty acids have been reported, few studies in rodents have reported

differences in serotonergic function. One exception (Kodas *et al*., 2004) found impairments in serotonin release that were residual from a vulnerable period of dietary deficiency of omega-3 HUFA. Rodent studies of neurotransmitter function, and behaviour affected by deficiencies in essential fatty acids, may never be sufficient models. Rodents have far less frontal cortex, less complex serotonergic neuronal circuitry linking frontal and limbic structures, and less complex associative cortex.

Deficient intakes of omega-3 fatty do appear to be linked to increased risks of suicide and self-harm. Among subjects hospitalized with major affective disorders, low plasma DHA at baseline (discharge from the hospital) was a robust predictor of new suicide attempts over the next 3 years. Low omega-3 status also distinguished suicide attempters from controls (Garland *et al*., 2007). In a randomized placebo controlled trial of 2 gm/day of EPA and DHA for 12 weeks, suicidal thinking, depression and the perception of life as a stressful experience were significantly reduced (Hallahan *et al*., 2007). Seasonal changes in EPA and DHA levels predict seasonal patterns in suicide death in Belgium which appear to be related to differences in serotonergic receptor binding (De Vriese *et al*., 2004). Given these findings, we sought to assess the proposition that increases in the apparent consumption of linoleic acid from seed oils might be associated with increased rates of suicide deaths.

Low EPA and DHA, high linoleic acid, and suicides

Here use utilized the same methodology and food commodity datasets as previously described in our examination of homicide mortality (Hibbeln *et al*., 2004). The United States Center for Disease Control age adjusted mortality database for suicide in the United States was used instead of homicide. A similar pattern of increased apparent consumption linoleic acid from seed oils correlating with an increased risk of suicide mortality from 1961–1999 was observed $r = 0.88$, $F = 174$, $p < 0.00001$ (non-adjusted linear regression). These results clearly do not reveal a causal relationship, nor do they indicate that linoleic acid consumption is the sole determinant of suicide risk. These results are however consistent with the observations that low omega-3 status increases risk of suicide and these do indicate that it would be reasonable to test the hypothesis that lowering linoleic acid intake many decrease suicide risk.

CONCLUSION

Evidence of positive effects of DHA and EPA on mental health, emotional feelings and behaviour, and of negative effects on these of linoleic acid, has now reached a level powerful enough to justify dietary and/or supplementation

trials on a wider scale. Trials would be into effects not just on individuals, but on social bonding and culture in neighbourhood or town areas. The importance of fish in many cultures and religions, as a symbol as well as a food, and also its essential role in evolution of the human brain as we know it, lead us to expect an emphatically positive effect.

DECLARATION

The Author has no conflicts of interest to declare.

REFERENCES

Conklin, S.M., Harris, J.I., Manuck, S.B., Yao, J.K., Hibbeln, J.R. and Muldoon M.F. (2007). Serum omega-3 fatty acids are associated with variation in mood, personality and behavior in hypercholesterolemic community volunteers. *Psychiatry Res*., **152**(1), 1–10.

Crawford, M.A., Ghebremeskel, K., Hibbeln, J.R., House, S., Hunter, D., Morley, D.C. *et al*. (2005). The Lancet and the Royal Society are both right and wrong. *Lancet*, **366**, 714–5.

Damasio, A.R. (1994). *Descartes' Error: Emotion, Reason, and the Human Brain*. New York: Putnam.

de la Presa Owens, S. and Innis, S.M. (1999). Docosahexaenoic and arachidonic acid prevent a decrease in dopaminergic and serotoninergic neurotransmitters in frontal cortex caused by a linoleic and alpha-linolenic acid deficient diet in formula-fed piglets. *J Nutr*., **129**, 2088–2093.

De Vriese, S.R., Christophe, A.B. and Maes, M. (2004). In humans, the seasonal variation in poly-unsaturated fatty acids is related to the seasonal variation in violent suicide and serotonergic markers of violent suicide. *Prostaglandins Leukot Essent Fatty Acids*, **71**, 13–8.

Dolan, R.J. (2002). Emotion, cognition, and behavior. *Science*, **298**, 1191–4.

Freeman, M.P., Hibbeln, J.R., Wisner, K.L., Brumbach, B.H., Watchman, M., Gelenberg, A.J. (2006a). Randomized dose-ranging pilot trial of omega-3 fatty acids for postpartum depression. *Acta Psychiatr Scand*., **113**, 31–5.

Freeman, M.P., Hibbeln, J.R., Wisner, K.L., Davis, J.M., Mischoulon, D., Peet, M. *et al*. (2006b). Omega-3 fatty acids: evidence basis for treatment and future research in psychiatry. *J Clin Psychiatry*, **67**, 1954–67.

Garland, M.R., Hallahan, B., McNamara, M., Carney, P.A., Grimes, H., Hibbeln, J.R. *et al*. (2007). Lipids and essential fatty acids in patients presenting with self-harm. *Br J Psychiatry*, **190**, 112–7.

Hallahan, B., Hibbeln, J.R., Davis, J.M. and Garland, M.R. (2007). Omega-3 fatty acid supplementation in patients with recurrent self-harm. Single-centre double-blind randomised controlled trial. *Br J Psychiatry*, **190**, 118–22.

Hamazaki, T., Sawazaki, S. and Kobayashi, M. (1996): The effect of docosahexaenoic acid on aggression in young adults. A double-blind study. *J Clin Invest*., **97**, 1129–1134.

Hamazaki, T., Sawazaki, S., Nagasawa, T., Nagao, Y., Kanagawa, Y. and Yazawa, K. (1999): Administration of docosahexaenoic acid influences behavior and plasma catecholamine levels at times of psychological stress. *Lipids*, **34**, S33–S37.

Hibbeln, J.R. (1998). Fish consumption and major depression. *Lancet*, **351**, 1213.

Hibbeln, J.R. (2001). Seafood consumption and homicide mortality. A cross-national ecological analysis. *World Review of Nutrition & Dietetics*, **88**, 41–6.

Hibbeln, J.R. (2002). Seafood consumption, the DHA content of mothers' milk and prevalence rates of postpartum depression: a cross-national, ecological analysis. *J Affect Disord*., **69**, 15–29.

Hibbeln, J.R., Davis, J.M., Steer, C., Emmett, P., Rogers, I., Williams, C. and Golding, J. (2007). Maternal seafood consumption in pregnancy and neurodevelopmental outcomes in childhood (ALSPAC study): an observational cohort study. *Lancet*, **369**, 578–85.

Hibbeln, J.R., Linnoila, M., Umhau, J.C., Rawlings, R., George, D.T. and Salem, N. Jr. (1998). Essential fatty acids predict metabolites of serotonin and dopamine in cerebrospinal fluid among healthy control subjects, and early- and late-onset alcoholics. *Biol Psychiatry*, **44**, 235–242.

Hibbeln, J.R., Nieminen, L.R., Blasbalg, T.L., Riggs, J.A. and Lands, W.E. (2006). Healthy intakes of n-3 and n-6 fatty acids: estimations considering worldwide diversity. *Am J Clin Nutr*., **83**, 1483S–1493S.

Hibbeln, J.R., Nieminen, L.R. and Lands, W.E. (2004). Increasing homicide rates and linoleic acid consumption among five Western countries, 1961–2000. *Lipids*, **39**, 1207–13.

Hibbeln, J.R. and Salem, N. Jr. (1995). Dietary polyunsaturated fatty acids and depression: when cholesterol does not satisfy. *Am J Clin Nutr*., **62**, 1–9.

Holman, R.T. (1998). The slow discovery of the importance of omega - 3 essential fatty acids in human health. *J Nutr*., **128**, 427S–433S.

Iribarren, C., Markovitz, J.H., Jacobs, D.R. Jr., Schreiner, P.J., Daviglus, M. and Hibbeln, J.R. (2004). Dietary intake of n-3, n-6 fatty acids and fish: relationship with hostility in young adults – the CARDIA study. *Eur J Clin Nutr*., **58**, 24–31.

Kodas, E., Galineau, L., Bodard, S., Vancassel, S., Guilloteau, D., Besnard, J.C. and Chalon, S. (2004). Serotoninergic neurotransmission is affected by n-3 polyunsaturated fatty acids in the rat. *J Neurochem*, **89**, 695–702.

Levant, B., Ozias, M.K. and Carlson, S.E. (2006a). Diet (n-3) polyunsaturated fatty acid content and parity interact to alter maternal rat brain phospholipid fatty acid composition. *J Nutr*., **136**, 2236–42.

Levant, B., Ozias, M.K. and Carlson, S.E. (2007). Specific brain regions of female rats are differentially depleted of docosahexaenoic acid by reproductive activity and an (n-3) fatty acid-deficient diet. *J Nutr*., **137**, 130–4.

Levant, B., Radel, J.D. and Carlson, S.E. (2006b). Reduced brain DHA content after a single reproductive cycle in female rats fed a diet deficient in N-3 polyunsaturated fatty acids. *Biol Psychiatry*, **60**, 987–90.

Maes, M., Mihaylova, I. and Leunis, J.C. (2005). In chronic fatigue syndrome, the decreased levels of omega-3 poly-unsaturated fatty acids are related to lowered serum zinc and defects in T cell activation. *Neuro Endocrinol Lett*., **26**, 745–51.

Mann, J.J., Oquendo, M., Underwood, M.D. and Arango, V. (1999). The neurobiology of suicide risk: a review for the clinician. *J Clin Psychiatry*, **60**, 7–11.

Mincke, E., Cosyns, P., Christophe, A.B., De Vriese, S. and Maes, M. (2006). Lower omega-3 polyunsaturated fatty acids and lower docosahexaenoic acid in men with pedophilia. *Neuro Endocrinol Lett*., **27**, 719–23.

Noaghiul, S. and Hibbeln, J.R. (2003). Cross-national comparisons of seafood consumption and rates of bipolar disorders. *Am J Psychiatry*, **160**, 2222–7.

Otto, S.J., de Groot, R.H. and Hornstra, G. (2003). Increased risk of postpartum depressive symptoms is associated with slower normalization after pregnancy of the functional docosahexaenoic acid status. *Prostaglandins Leukot Essent Fatty Acids*, **69**, 237–43.

Pavlov, I.P. (1951). [Conditioned reflex.]. *Feldsher Akush*, **11**, 6–12.

Reis, L.C. and Hibbeln, J.R. (2006): Cultural symbolism of fish and the psychotropic properties of omega-3 fatty acids. *Prostaglandins Leukot Essent Fatty Acids*, **75**, 227–36.

Sinclair, A.J., Begg, D., Mathai, M. and Weisinger, R.S. (2007). Omega 3 fatty acids and the brain: review of studies in depression. *Asia Pac J Clin Nutr*., **16** Suppl., 391–7.

Skinner, B.F. (1938). *The Behavior of Organisms*. New York: Appleton-Century-Crofts.

Tanskanen, A., Hibbeln, J.R., Hintikka, J., Haatainen, K., Honkalampi, K. and Viinamäki, H. (2001a). Fish consumption, depression, and suicidality in a general population. *Arch Gen Psychiatry*, **58**, 512–513.

Tanskanen, A., Hibbeln, J.R., Tuomilehto, J., Uutela, A., Haukkala, A., Viinamäki, H. *et al*. (2001b). Fish Consumption and Depressive Symptoms in the Population. *Psychiatric Services*, **52**, 529–531.

Thienprasert, A., Hamazaki, T., Kheovichai, K., Samuhaseneetoo, S., Nagasawa, T. and Wantanabe, S. (2000). The effect of docosahexaenoic acid on aggression/hostility in elderly subjects: A placebo-controlled double blind trial. (abstract). Tsukuba, Japan: 4th Congress of the International Society for the Study of Lipids and Fatty Acids, p. 189.

Zanarini, M.C. and Frankenburg, F.R. (2003). Omega-3 fatty acid treatment of women with borderline person-ality disorder: a double-blind, placebo-controlled pilot study. *Am J Psychiatry*, **160**, 167–9.