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Exclusive Sneak Peek

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Table of Contents

Paying attention to omega-3s for ADHD

Reduced Symptoms of Inattention After Dietary Omega-3 Fatty Acid Supplementation in Boys with and without Attention Deficit/Hyperactivity Disorder

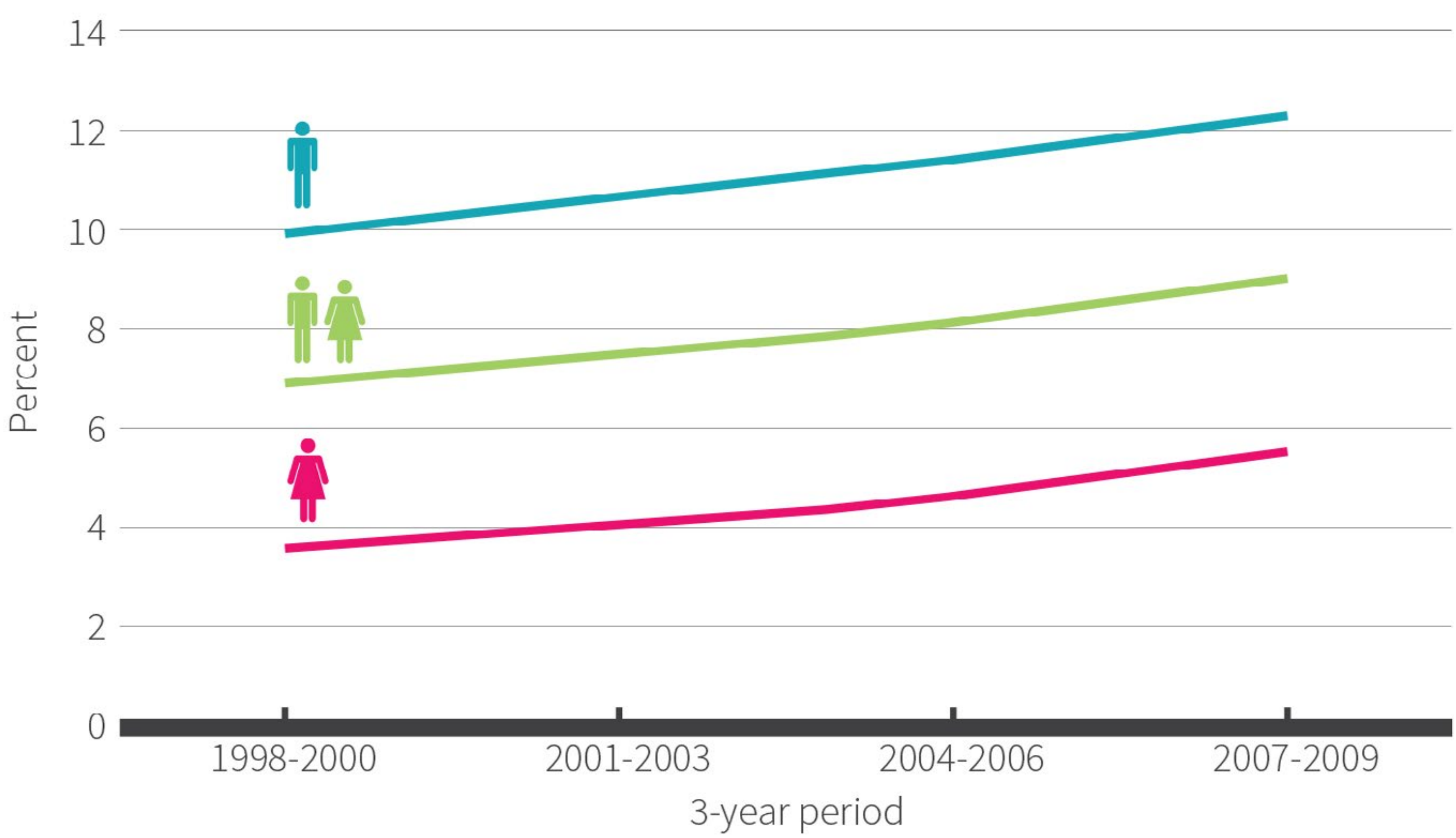
Introduction

If you skim the headlines of major research journals, sometimes it seems like there's nothing that omega-3s can't do. Other times, they seem overrated. Since this is the fourth time ERD has covered omega-3 fatty acids in recent history, we won't bore you with too many details. But, in case you missed it, here's a very brief primer:

Omega-3 fatty acids are named for their double bond (making the fatty acid "unsaturated," since it has fewer hydrogen atoms than the maximum) that is three carbons from the omega, or end of the chain. Omega-3s are found in fish and some plants, like flax and walnuts. Both of the omega-3s used in this study, docosahexaenoic acid (DHA) and eicosapentaenoic acid (EPA) come from fish sources rather than plants, and are critical for early brain development. These fatty acids are added to many commercial baby formulas, to mimic the high levels found in breastmilk.

The study under review examined the effects of omega-3 supplementation on the symptoms of Attention Deficit/Hyperactivity Disorder (ADHD). Formerly known as ADD or Attention Deficit Disorder, the 1987 revision of the gold standard for psychiatric and mental disorders, known as the Diagnostic and Statistical Manual, relabeled the disorder ADHD. An additional revision in 1994 classified patients into either the 'hyperactive-impulsive' subtype, 'inattentive' subtype, or 'combined' subtype based on their specific symptoms. ADHD is one of the most commonly diagnosed childhood disorders, affecting as many as 11% of children in the U.S., or about 6.4 million. The increasing prevalence of ADHD is shown in Figure 1. Medications for ADHD are primarily (and perhaps paradoxically) central nervous system stimulants, with methylphenidate being the most commonly prescribed drug. One of the hypothesized causes of ADHD is lower dopamine production, which may result in unnecessary firing of neurons that are unrelated to the task the brain is trying to complete.

Figure 1: Prevalence of children aged 5-17 diagnosed with ADHD in the US



Source: CDC/NCHS, Health Data Interactive and National Health Interview Survey.

The drug allows the decreased levels of dopamine and norepinephrine in the brain to be used more effectively because it blocks reuptake receptors, thus enhancing the functionality of the neurons in the prefrontal cortex that are responsible for cognitive function.

Attention Deficit/Hyperactivity Disorder, or ADHD, is one of the most commonly diagnosed childhood disorders, affecting as many as 6.4 million children in the US. The most commonly prescribed drug for ADHD, methylphenidate, affects the levels of dopamine, norepinephrine, and serotonin in the brain to alleviate symptoms of distraction.

Who and what was studied?

Forty boys living in the Netherlands, ages eight to 15 and diagnosed with ADHD, were recruited for the study, and are referred to from here on as the ADHD group. Most of the participants were taking methylphenidate at the time of enrollment and were permitted to continue taking the medication as prescribed for the duration of the study, other than a 24 hour washout period prior to the fMRI scans. An additional 39 boys without ADHD were also enrolled as matched participants for age, BMI, and hand preference, and were referred to in the study as the Reference Group (RG). Within each group, half of the participants were randomly assigned to consume 10 grams daily of a margarine product with added omega-3 fatty acids, with 650 milligrams each of DHA and EPA per serving. This was denoted as the 'active' arm of each group. The other half of each group was assigned to the 'placebo' arm and consumed 10 grams of margarine that contained monounsaturated fatty acids `instead of omega-3 fatty acids. The two products were otherwise identical in saturated fatty acid and omega-6 fatty acid contents.

The participants consumed their assigned margarine product for a total of 16 weeks, during which they were told to avoid other omega-3 supplements or fortified products, and limit fatty fish to one serving per week to prevent additional omega-3 consumption from interfering with the study intervention.

Two behavioral assessments for symptoms of ADHD were used in this study, both completed by the parents of the participants. The first, the Child Behavior Checklist (CBCL), asks parents on a scale of zero to two to assess their child's various negative behaviors. This is used as a diagnostic and assessment tool for a number of disorders, including ADHD. Higher scores indicate more frequent displays of negative behavior. The behaviors can also be analyzed in subsets of various categories. This study focused on the Attention

Methylphenidate's Mechanism of Action

Prescribing a stimulant for someone who is already hyperactive seems contradictory. In fact, methylphenidate (which goes by a variety of names, including Ritalin and Concerta) and other similar stimulants were prescribed for ADHD for decades before a mechanism of action was determined. It's typically only at higher doses than what is prescribed for ADHD that the stimulant effects gain the upper hand. At lower doses, the drug helps coordinate the actions of dopamine, norepinephrine, and to a lesser extent, serotonin, by preventing them from being taken back up by receptors in the brain. The increased effect of dopamine helps the brain focus on tasks, while the effects on norepinephrine may improve the brain's normal reward cycle for completing tasks. The stabilized serotonin may also help produce a sense of well-being and calm.

Problems, Rule Breaking, and Aggressive Behavior subcategories of behaviors. The CBCL was used as the primary outcome measure over the course of the entire study. The second test was the Strengths and Weaknesses of ADHD symptoms and Normal behavior scale (SWAN). This assessment was conducted roughly every four weeks throughout the study, and was used as a secondary measure to assess changes in behavior over time. SWAN asks the parent to assess the frequency of a child's positive behaviors, such as paying attention to details, waiting their turn, and playing quietly.

The participants completed an fMRI task to assess response inhibition at the start of the study and at the follow-up appointment at the end of the study. The participants were asked to alternately press and hold a button when told, or not press a button when told not to. This test measures whether the button is pressed at the correct times to assess the participant's ability to control their motor impulses, one of the symptoms of ADHD. Participants also provided urine and cheek swab samples, and completed a dietary questionnaire to evaluate existing fatty acid deficiencies. The urine samples were used to test for markers of dopamine levels in the brain in order to measure dopamine turnover, and the cheek swabs were tested for omega-3 levels in the fatty acids of the cell membranes as a measurement of compliance. In addition to the CBCL and SWAN behavioral assessments previously described, an attempt was also made to collect data from the teachers of participants before and after the study. However, the data were unable to be used due to a low response rate.

“There were no differences in fMRI performance in any of the groups, compared to their baseline results.”

At three intervals during the course of the study, parents completed the SWAN behavioral assessment and a dietary checklist to assess compliance. To further assess compliance over the course of the study, the remaining margarine product was weighed at the end of the study, and the amount of DHA incorporation into cell membranes collected in the cheek swab samples was measured and compared to baseline measurements.

Forty boys with ADHD and 39 boys without any diagnosed disorders were randomly assigned to consume normal margarine or margarine with 650 milligrams each of added DHA and EPA for 16 weeks. At the beginning and end of the study, they completed a fMRI task to assess impulse control, and their parents completed behavioral questionnaires.

What were the findings?

The researchers discussed three sets of findings from the study: behavioral, as assessed by the CBCL and SWAN questionnaires; physiological, looking at the dietary assessment for the presence of fatty acid deficiencies, the urinalysis data, and the incorporation of omega-3 fatty acids in the cheek cells of the ‘active’ groups; and neurological, from the fMRI data. There were no differences in fMRI performance in any of the groups, compared to their baseline results.

Based on the behavioral data, both the ADHD and the RG participants showed improvements in their overall scores on the CBCL after consuming the omega-3 supplemented margarine product for 16 weeks. However, only the ADHD participants showed improvements in the Attention Problems subset of behaviors, with an average decrease of 1.83 points on their checklist score. There were no differences in the Rule Breaking or Aggressive Behavior subsets for any group. The data were then reanalyzed without the seven participants who had increased their medication dose during the course of the study to rule out the possible effects of a higher dose of medication, and the decrease remained statistically significant. There were no statistically significant differences reported on the SWAN scores.

The physiological data showed that at baseline, children in the ADHD group were more likely to show symptoms of fatty acid deficiencies, although only four of the 79 participants actually met the cutoff for a defined deficiency. Analysis of the cell membranes of cheek cells collected after the treatment period showed higher levels of DHA in the group that consumed the omega-3 margarine compared to the group that consumed regular margarine. There was a slight but statistically significant correlation between CBCL scores and DHA levels both before and after omega-3 treatment in the ADHD group. That is, the lower the level of DHA measured in the cheek cells, the higher the child tended to score on the negative behavior assessments. The urine samples were analyzed for homovanillic acid, a marker for dopamine levels in the brain, but no differences were observed in any of the groups. This finding refutes the hypothesis that the effects of the omega-3 supplements were caused by changes in the metabolism of dopamine.

Both groups experienced some behavioral improvements after consuming added DHA and EPA for 16 weeks, but only participants with ADHD specifically experienced improvements in attention. Omega-3 supplementation did not have any effects on performance of a fMRI task measuring control of cognitive responses, and did not affect levels of dopamine in the brain, as measured by a marker in urine samples.

What does the study really tell us?

There are two important limitations to note in this study. First, a participant only had to consume two-thirds or more of the assigned margarine product (based on comparing the weight of the returned product with the starting weight) and was permitted to skip consuming the product for up to seven days while still being considered compliant with the study protocol. This lack of rigorousness to the study protocol may have contributed to the smaller effects seen in the study. Second, the researchers noted after additional statistical analysis that the sample size of the study would have needed to be almost ten times larger to show any effects of treatment in the fMRI task.

This study was supported by Unilever, manufacturers of a number of nutrition, health, and food products worldwide. In addition to producing the supplemented margarine for the study, Unilever also funded the trial (including funding the researchers who were conducting the trial), participated in the study design, and employs two of the co-authors on the paper. Many companies do produce rigorous science, and a complete lack of corporate interests is no guarantee that the reported results are valid or worthwhile, which is why it's just something to note when evaluating any study. Since the study was double blinded, none of the study researchers knew which child had received which product until after the study was completed.

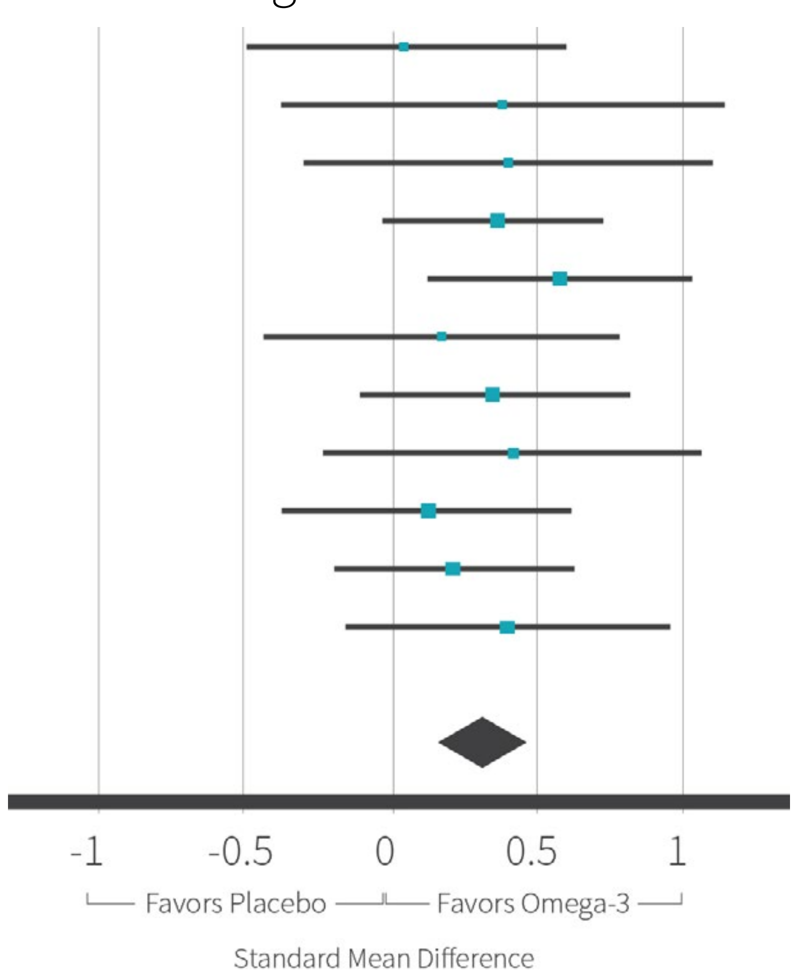
Nevertheless, the main result, which is an overall improvement in behavioral measures in both groups and a specific improvement in attention problems in the ADHD group (both on the order of about 15%) provides some evidence for the efficacy of EPA and DHA supplementation for boys with ADHD. These effects are most likely only seen in conjunction with medication — 95% of the ADHD study participants were taking methylphenidate during the trial, so no conclusions can be drawn about the effects of omega-3s on the symptoms of ADHD in the absence of standard therapies.

Two limitations of the study include the relatively low threshold for compliance and the lack of statistical power for the functional MRI task. In addition, the study had significant corporate support. The industry researchers were involved in the overall study design, but the fact that the study was double-blinded reduces the risk of biases in analyzing the data.

The big picture

A number of observational studies have previously reported lower omega-3 fatty acid levels in children with ADHD. Yet clinical trials where omega-3s are given as an intervention have shown minimal or no advantage for supplementation for selected ADHD symptoms. As shown in Figure 2, meta-analysis of

Figure 2: Meta-analysis of clinical trials of omega-3's effects on ADHD



Reference: Bloch MH, et al. J Am Acad Child Adolesc Psychiatry. 2011 Aug.

pertinent trials suggest that effects, if any, are small, and supplementation may only be useful in conjunction with medication. A separate study indicated that when children took both medication and omega-3 supplements, they needed lower doses of medication to achieve symptom improvements. The ratio of DHA to EPA may also be critical for treatment success, since earlier studies had a low ratio of DHA to EPA, whereas this study used equal amounts.

In this context, it is also worth mentioning that supplementation of omega-3 fatty acids in general seems to have positive effects on developing brains. Thus, it is not surprising that behavioral improvements were seen in both the ADHD and the RG arms of this study. Whether these behavioral improvements are mediated by changes in the level or effects of dopamine in the brain requires further study. The urine levels of homovanillic acid, the dopamine metabolite, measured in this study point to a different mechanism, but a more direct evaluation of the effects on the brain would be required to disprove this hypothesis. Instead, it's possible that the effects that were specific to the ADHD participants could be due to improved neuronal function, as has been previously demonstrated.

The magnitude of the effects observed in the study under review was relatively low. This is in line with the results of previous meta-analyses that indicate small treatment effects. This study is also consistent with previous research suggesting that omega-3 supplementation may only be effective in conjunction with medication for treatment of ADHD symptoms.

Frequently asked questions

Why was the study conducted only on boys?

The authors chose to only recruit boys for the study for two reasons. The prevalence of ADHD is two to three times higher in boys than in girls, so enrollment was simpler. The researchers also wanted to eliminate gender as a confounder for the fMRI studies. However, this means that the study results cannot be extrapolated to girls with ADHD.

It would be interesting to see a separate study done in girls, since girls who are diagnosed tend to have different symptoms than boys. Girls tend to display more "internalizing" symptoms such as separation anxiety, whereas boys tend to exhibit more "externalizing" symptoms like aggression and impulsivity — so it's possible that the omega-3 supplementation could affect them in very different ways.

Why didn't the treatment affect the dopamine pathway, when there is so much evidence that dopamine is dysregulated in ADHD?

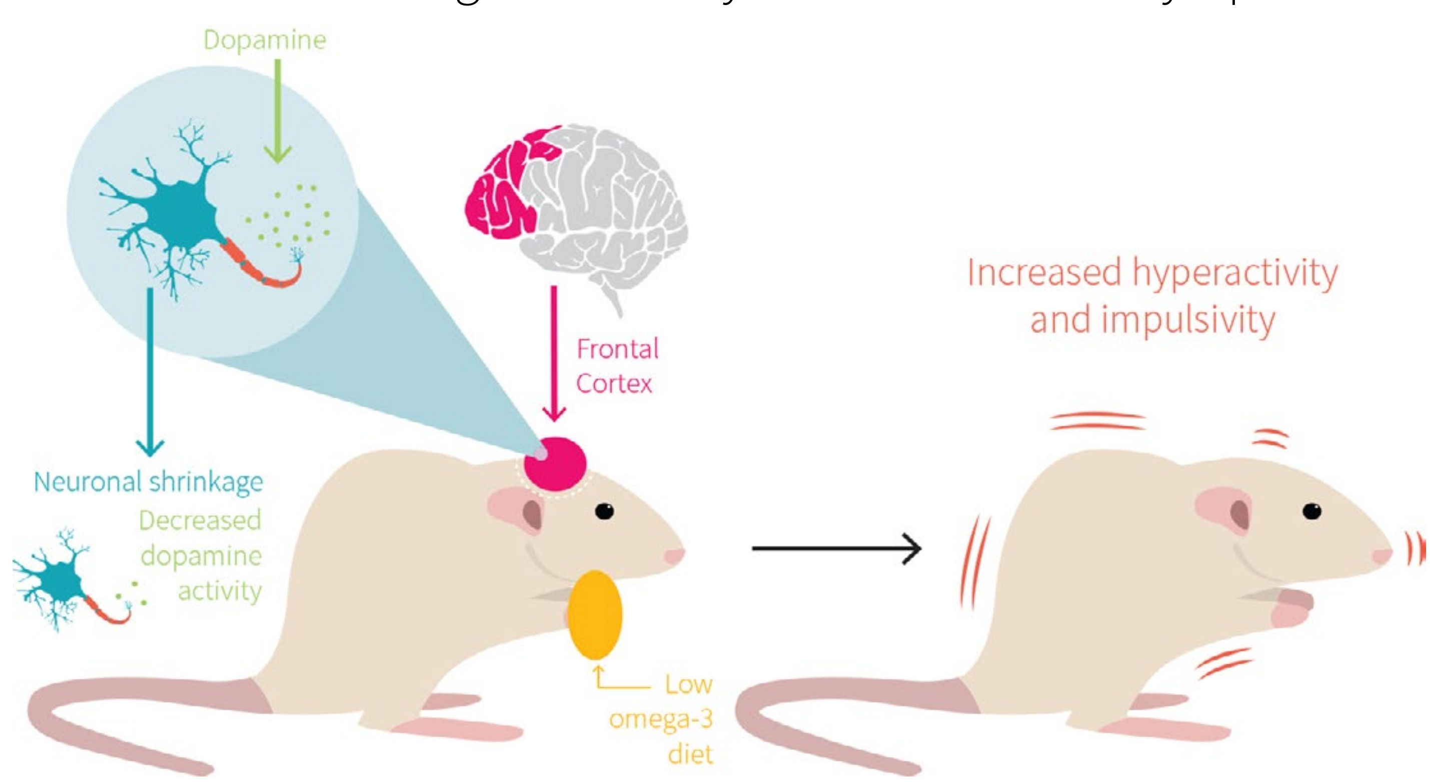
Dopamine has been implicated in the control of cognitive functions, particularly in children with ADHD. Mechanistic evidence in rats has provided some clues as to what may be going on in humans, as depicted in Figure 3. One of the challenges in this study may be in the measurement of homovanillic acid, which can sometimes produce unreliable results on dopamine and its effects. It's possible that effects could have been overlooked when an indirect marker for dopamine activity was measured. The brain is a complex system, and it's also possible that omega-3s may play more of a role in the cell membranes of neurons rather than the signaling pathways themselves.

What should I know?

Supplementing with omega-3 fatty acids in margarine resulted in some modest behavioral improvements in boys both with and without diagnosed ADHD. Only boys with ADHD (who were also mostly on medication) experienced specific improvements in attention. Based on the data from the study under review, it appears that this effect was not mediated by the effects of dopamine on cognitive control. There were also no differences between the groups in a functional MRI task, which further weakens the hypothesis that the behavioral effects of omega-3 supplements are mediated by changes in the level of metabolism of dopamine. ◆

To discuss this study, visit the ERD Forum on Facebook, and for more (and more) information on omega-3 fatty acids, check out the extensive work that's gone into the Examine.com page on fish oil.

Figure 3: How a low omega-3 diet may induce ADHD-like symptoms in rats



Reference: Bos DJ, et al.Neuropsychopharmacol. 2015 Apr.