



## Review

## Can $\omega$ -3 fatty acids and tocotrienol-rich vitamin E reduce symptoms of neurodevelopmental disorders?



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### ABSTRACT

The incidence of childhood neurodevelopmental disorders, which include autism, attention-deficit hyperactivity disorders, and apraxia, are increasing worldwide and have a profound effect on the behaviors, cognitive skills, mood, and self-esteem of these children. Although the etiologies of these disorders are unclear, they often accompany genetic and biochemical abnormalities resulting in cognitive and communication difficulties. Because cognitive and neural development require essential fatty acids (particularly long-chain  $\omega$ -3 fatty acids often lacking in mother's and children's diets) during critical growth periods, the potential behavior-modifying effects of these fatty acids as "brain nutrients" has attracted considerable attention. Additionally, there is compelling evidence for increased oxidative stress, altered antioxidant defenses, and neuroinflammation in these children. The purpose of this review is to provide a scientific rationale based on cellular, experimental animal model, observational, and clinical intervention studies for incorporating the combination of  $\omega$ -3 fatty acids and tocotrienol-rich vitamin E as complementary nutritional therapies in children with neurodevelopmental disorders. Should this nutritional combination correct key clinical or biochemical outcomes and/or improve behavioral patterns, it would provide a safe, complementary option for these children.

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### Introduction

Apraxia, autism, and attention-deficit hyperactivity disorder (ADHD) encompass a spectrum of neurodevelopmental disorders (NDD) affecting children and adults. Apraxia is a poorly understood, multisymptomatic, speech sound disorder characterized by a child's inability to form sounds and words [1,2]. Autism is generally characterized by varying degrees of dysfunctional social and communicative abilities; and ADHD is associated with difficulty focusing, inattention, hyperactivity, and impulsivity. The incidence for autism in children is approximately 1% in the United States [3], whereas estimates for ADHD range from 6.5% to 11% among children ages 5 to 15 y [4]. Data for children suffering with apraxia are more difficult to ascertain; a study estimating diagnostic outcomes in >12,000 children referred with speech delay of unknown origin found that 3% to 4% of these children were classified as apraxic [5]. Because several of these NDD exhibit comorbidity and overlapping

cognitive, behavioral, and speech motor skill deficits, simple diagnosis is frequently difficult.

Currently, the underlying causal factors implicated in the pathogenesis of NDD are unknown. However, alterations or dysfunction of several pathways have been implicated, including:

1. neurologic impairment caused by infection, illness, or injury;
2. atypical gene/environmental interactions;
3. complex neurodevelopmental disorders (possibly as a secondary response to genetic or metabolic conditions);
4. immunologic abnormalities; and
5. mitochondrial diseases.

It also has been speculated that NDD are influenced by environmental factors such as exposure to pollutants or toxins, reduced antioxidant defense mechanisms, and in cases of apraxia, possible malabsorption syndromes [6]. Currently, the most prescribed treatments for these disorders include tedious speech and motor therapies, psychotherapies, stimulants, and the antipsychotic prescription drug risperidone; in many cases, particularly autism, these treatments fail to improve

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symptomology [7]. Clearly, additional clinical and basic scientific research into the cause(s) of childhood NDD is warranted to develop effective, safe, and optimal therapeutic options for the children and families afflicted.

Interestingly, from a brain-behavior perspective, the disturbances of perception, attention, and behavior found in children afflicted with these disorders reveal parallels with observed symptoms of fatty acid deficiency, especially  $\omega$ -3 fatty acids. When these fatty acids are inadequately obtained in utero via the maternal diet, neurologic development is significantly effected [8]. The unique biological properties of  $\omega$ -3 fatty acids and their specific function in neurologic and brain development has led to increased focus on their clinical potential in neurologic and psychiatric disorders. Moreover, both oxidative stress and neuroinflammation have been demonstrated in children with NDD. Requirement for additional vitamin E is also recommended in the presence of additional  $\omega$ -3 fatty acids as an increased dietary intake of polyunsaturated fatty acids increases the requirement of vitamin E [9]. Therefore, considering the SECS (“safe, easy, cheap and sensible”) criteria [10], we hypothesize that tocotrienol (T3)-rich vitamin E, a particularly biologically active form of vitamin E, in conjunction with  $\omega$ -3 fatty acids, may provide a novel and safe therapeutic approach benefitting children diagnosed with NDD.

### $\omega$ -3 fatty acids: Benefits in neuroinflammation

Several studies have documented lower  $\omega$ -3 fatty acid concentrations in children with NDD versus healthy controls [11,12], and although associations between maternal  $\omega$ -3 fatty acid intake and cognitive development are conflicting [13,14], the overall importance of adequate maternal and childhood dietary intake of  $\omega$ -3 fatty acids from both animal and human studies is highly suggestive. The relationship between circulating  $\omega$ -3 fatty acid concentrations and ADHD was recently extended when an association was reported between erythrocyte  $\omega$ -3 content and ADHD in children with learning difficulties versus those children with ADHD but no learning difficulties [15]. A recent review [16] also noted that blood concentrations of docosahexaenoic acid (DHA) were associated with brain structural and functional aspects of neuropsychiatric disorders. Because of results from these studies reporting reduced or altered long-chain fatty acid metabolism in NDD, several investigators have evaluated the potential clinical benefits of these fatty acids with frequently promising results. For example, two studies [17,18] demonstrated clinical benefits of  $\omega$ -3 fatty acids, with or without other vitamins or fatty acids, in autistic children. An open-labeled study (2009) collected self-reports from parents administering  $\omega$ -3 fatty acids and vitamin E to children with apraxia. The study found that 97% of families participating reported significant improvements in cognitive, behavioral, and gastrointestinal symptoms [6]. Although these were only testimonial data, the observed changes noted by the parents give hope that these nutrients may, in fact, decrease the severity of the NDD symptoms. Other studies failed to demonstrate improvement in children with ADHD [19,20]. Nevertheless, most studies have found that supplementation with  $\omega$ -3 fatty acids not only normalizes  $\omega$ -3 fatty acid status through cellular enrichment, but also provides evidence of clinical improvements in the problematic behavioral patterns characteristic of many children with NDD. As important, no serious adverse events have been reported in these studies, which is consistent with general observations in adults [21]. Nevertheless, potential incorporation of  $\omega$ -3 fatty acid supplements in childhood NDD must be carefully considered in the

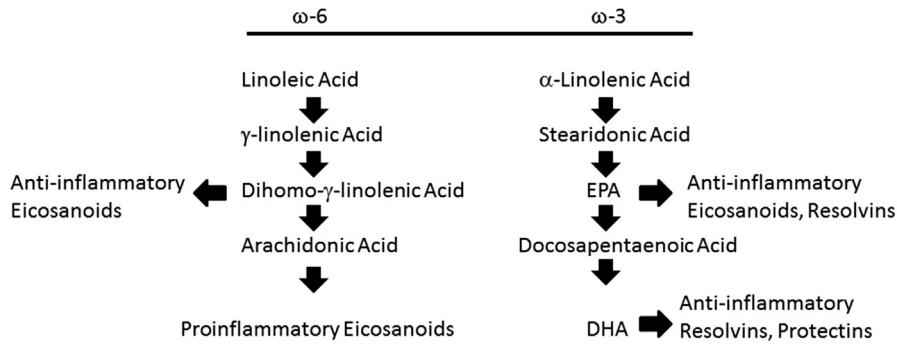
absence of any long-term safety evaluation in these children. Clearly, children consuming these supplements should be under physician supervision, particularly if the child is also prescribed anticoagulants.

From a biochemical and physiological perspective, there are at least three well-established pathways providing a solid biochemical and physiological rationale for including  $\omega$ -3 fatty acids as a complementary nutritional component in the treatment of NDD: 1) as structural modifying components interacting with membrane phospholipids, 2) as precursors to eicosanoid or oxidatively modified products, and 3) as effectors of nuclear transcription factors and/or receptor agonists or antagonists (Fig. 1). The import of  $\omega$ -3 fatty acids in each of these is considered briefly.

First, the importance of  $\omega$ -3 fatty acids in neural and brain tissues is strongly suggested by membrane enrichment in these tissues. DHA comprises 15% to 20% of the total fatty acids in adult frontal cortex [22] and upward of 50% of total polyunsaturates in neural tissues [23]. This enrichment plays an essential role in assuring the correct environment for membrane protein function and membrane order (fluidity) [24].  $\omega$ -3 fatty acids increase membrane fluidity and permeability [25], effects that may influence cell signaling activation pathways via cholesterol: Lipid raft perturbations [26].  $\omega$ -3 fatty acid deficiency promotes several deleterious effects related to brain and neurologic function, including inhibition of brain maturation and neuroplasticity, abnormalities in neurotransmitter function, and persistent adverse developmental outcomes if deficiency occurs during neural development [27,28].

Second, fatty acid pools are directly influenced by dietary fatty acid intake. Dietary supplementation with fish oil results in an increased proportion of eicosapentaenoic acid (EPA) and DHA within biological membranes, frequently at the expense of arachidonic acid (AA). When dietary  $\omega$ -3 levels are low, an imbalance of proinflammatory eicosanoids may occur as eicosanoids such as prostaglandins, thromboxanes, and other oxidative metabolites derived from AA, facilitate neuroinflammation [29]. Additionally, EPA and DHA are metabolized to resolvins and protectins, which are very potent anti-inflammatory mediators in cellular and animal model systems [30,31]. With evidence for brain inflammation in autism [32,33], these anti-inflammatory and neuroprotective effects of the  $\omega$ -3s in childhood NDD provide very intriguing mechanistic avenues for further investigation. To our knowledge, there is no data for the cellular or tissue production of these lipid mediators in NDD. Finally, clinical significance should also be considered for inclusion of the  $\omega$ -6 fatty acid,  $\gamma$ -linolenic acid [34]. Unlike eicosanoids derived from AA, this fatty acid is metabolized to eicosanoids such as prostaglandin E1 (PGE<sub>1</sub>) and 15-hydroxy-PGE<sub>1</sub> [35], lipid mediators that also have potent anti-inflammatory effects. Indeed, this is the most likely reason several investigators have chosen this fatty acid for adjunct supplementation along with  $\omega$ -3 fatty acids in children with NDD.

The final, and least explored, pathway by which  $\omega$ -3 fatty acids may modulate biochemical and physiological responses implicated in NDD is via their effects on nuclear transcription factors, especially those involved in immunologic dysfunction. In vitro neuronal cell studies reveal DHA to be a potent ligand for peroxisome proliferator-activated receptor  $\gamma$  (PPAR $\gamma$ ), which results in a suppression of proinflammatory genes encoding for various interleukins and tumor necrosis factor (TNF)- $\alpha$  [36,37]. Via this same PPAR $\gamma$ -dependent activation pathway, DHA has also been shown to inhibit activation of another transcription factor, nuclear factor (NF)- $\kappa$ B, a key regulatory protein responsible for stimulating expression of proinflammatory genes



**Fig. 1.** Essential fatty acid metabolism and metabolites.  $\omega$ -3 fatty acids (EPA and DHA) are metabolized to less or anti-inflammatory eicosanoids (3-series) or to potent neuroprotective metabolites (Resolvins and Protectins). The  $\omega$ -6 fatty acid dihomogamma-LA can be similarly metabolized to anti-inflammatory lipid mediators.

including cytokines, cyclooxygenase, and inducible nitric oxide [29]. Furthermore, the immunomodulatory effects and clinical implications of  $\omega$ -3 fatty acids in childhood NDD should be considered in lieu of evidence for elevated TNF- $\alpha$  in the cerebrospinal fluid [38], and the elevated expression of interleukin-6 in brains from autistic children [39]. Indeed, significant evidence for neuroinflammation and oxidative stress in the brains of autistic children has been reported from several laboratories [40–42] confirming neuroinflammation may be a major pathogenic response during NDD.

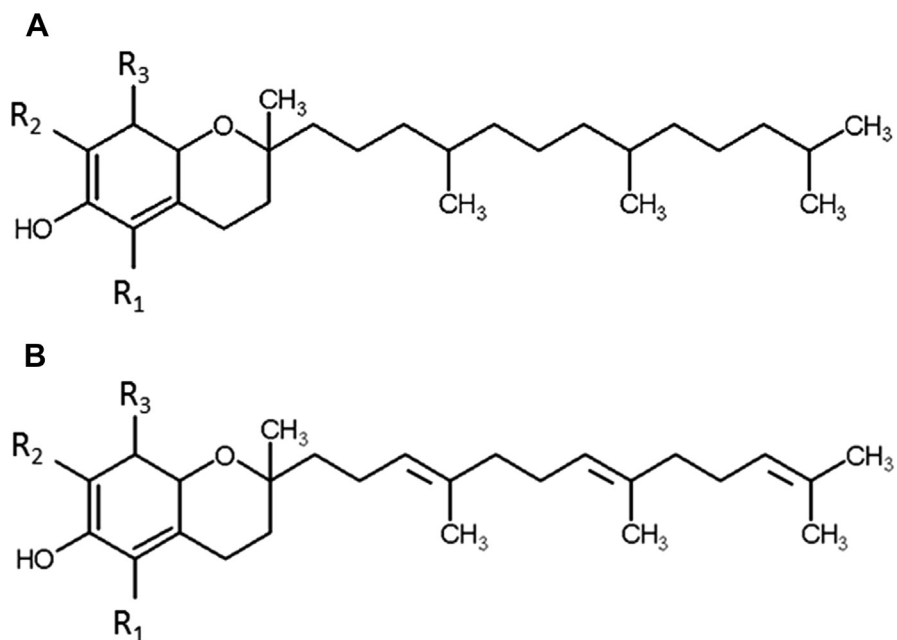
The safety profile of  $\omega$ -3 fatty acids, their promising clinical responses, and their well described anti-inflammatory effects warrant continuing investigation for use as an adjunctive, complementary nutritional therapy in children affected by NDD.

#### Oxidative stress, neuroprotection, and the potential benefits of tocotrienol-rich vitamin E

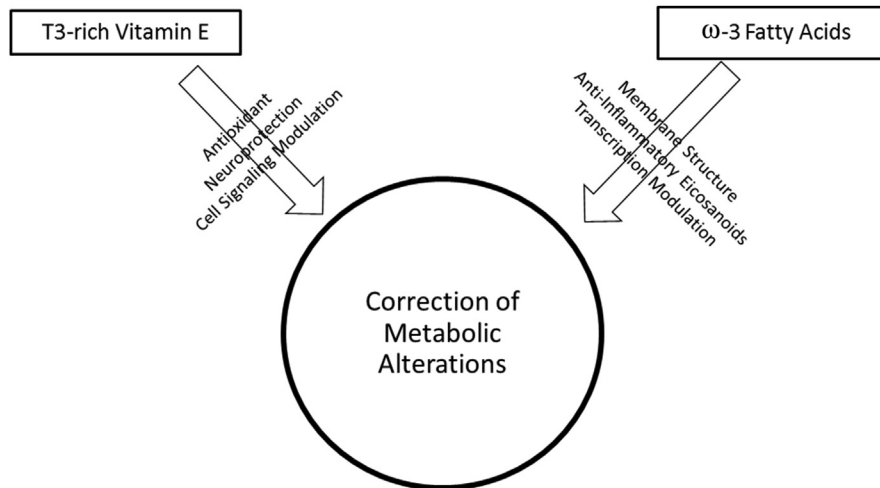
Along with demonstrated improvements by  $\omega$ -3 fatty acids on some behavioral and biochemical parameters in children with NDD, there is also extensive literature suggesting increased oxidative stress occurs in children with NDD [43–45]. As a corollary to these findings, other researchers found reduced

antioxidant defenses [46,47]. One study reported reduced antioxidants (glutathione peroxidase and superoxide dismutase) in autistic children and concluded, “Autistic children might benefit from antioxidants supplementation coupled with polyunsaturated fatty acids” [17]. Relatedly, a recently published study [48] found impaired glutathione biosynthesis in the brains of autistic children.

There is also evidence for reduced plasma levels of vitamin E in children with NDD. In a recent review [49], researchers noted that in three studies where vitamin E levels were measured, all the studies found consistently lower vitamin E concentrations in autistic children. In contrast, an open-labeled study [6] reported that 10 of 13 children measured for vitamin E status were considered sufficient; however, as commented by the authors, it was unknown whether these plasma levels truly reflected brain and neural tissue concentrations of  $\alpha$ -tocopherol (TH) or whether these individuals had adequate cellular uptake mechanisms and/or efficient vitamin E transport mechanisms (see later). These data, in conjunction with reduced glutathione levels in individuals with autism overall [50], clearly suggest that neuronal oxidative stress and antioxidant defense deficiencies are likely pathways effected during childhood NDD.



**Fig. 2.** The structure of vitamin E: A) tocopherols and B) tocotrienols.



**Fig. 3.** Rationale and hypothesized mechanisms for potential benefits of nutritional intervention with combination of  $\omega$ -3 fatty acids and T3-rich vitamin E for improving symptoms of children with NDD.

Thus, the combination of elevated oxidative stress and reduced vitamin E levels in children with NDD strongly suggests a need for both vitamin E and  $\omega$ -3 fatty acids as a complementary nutritional therapeutic intervention in these children. The primary function of vitamin E is as the major lipid-soluble, chain-breaking antioxidant in mammalian systems serving to protect membrane polyunsaturated fatty acids against oxidative damage (for a recent review on vitamin E see [51]). This protective role for vitamin E is particularly important in highly  $\omega$ -3 fatty acid-enriched neurologic tissues. Interestingly, children with NDD may frequently present neurologic symptoms overlapping with those observed in vitamin E-deficient patients [52], although frank human vitamin E deficiency is limited to individuals with either severe malnutrition or fat malabsorption syndromes, such as children with cystic fibrosis or cholestatic liver disease [52], or in humans carrying a genetic mutation in the gene encoding for  $\alpha$ -TTP [53].

Vitamin E is a family of 8 naturally occurring compounds: Four THs and four T3s (Fig. 2). THs contain a long phytyl side chain, whereas T3s contain unsaturated isoprenylated units. Both forms of vitamin E are also designated according to the location and number of methyl groups on the chromanol ring ( $\alpha$ ,  $\beta$ ,  $\gamma$ ,  $\delta$ ). From a nutritional and physiological perspective,  $\alpha$ -TH is the most important form of the vitamin, largely through mechanisms that favor its transportation and retention in the circulation: Its greater binding affinity toward the  $\alpha$ -TH transfer protein ( $\alpha$ -TTP), the protein most responsible for preferential retention of  $\alpha$ -TH and discrimination against the other forms of the vitamin [53], and its reduced metabolism through cytochrome P450 and  $\beta$ -oxidation pathways to its water-soluble metabolites [54]. Consequently, under normal dietary intake, T3 was not thought to contribute health benefits. Furthermore, dietary sources of T3 are quite limited, with oils from rice bran and red palm being major sources. However, despite the body's poor absorption of T3, human studies have found that it is widely distributed in tissues and plasma upon supplementation [55,56]. Knowing that this form of vitamin E can traverse membranes and enter tissues such as the brain combined with *in vitro* data suggesting strong antioxidant activity, there is now a growing literature supporting potential benefits of T3.

The potential of this form of vitamin E to effect brain development, oxidation, and neuroprotection is quite exciting. Although there are clinical studies under way (personal communication with Dr. Tan May Loong, Penang Medical College, Malaysia;

Tocotrienols for School-going Children with ADHD, NCT01855984), to our knowledge no data yet exists to evaluate T3 supplementation in children with NDD. Nonetheless, there are extensive preclinical and clinical observations warranting a closer evaluation of T3 supplementation as a potential adjunct therapy in these children. Like the SECS criteria described for  $\omega$ -3 fatty acids, our scientific rationale for inclusion of T3-rich vitamin E is attributed to a combination of factors: 1) their safety profile in the presence of either ineffective or potentially toxic pharmaceutical agents; 2) their antioxidant properties; and perhaps most relevant for children with NDD, 3) their demonstrated neuroprotective and neuro-restorative effects in preclinical models of neurodegeneration [57, 58]. From a safety evaluation, T3 from palm oil (the primary source) was given Generally Recognized As Safe status in 2009. According to our research, there are no reports of serious adverse events in adults supplemented with T3. However, like virtually all dietary supplements, there are no long-term studies examining the effects of T3 supplementation in children. Although both TH and T3 are efficient membrane antioxidants, *in vitro* evidence suggests that T3 is a more potent antioxidant by virtue of its greater membrane mobility [59,60]. Of more relevance, however, to *in vitro* antioxidative effects, are results from clinical studies reporting a reduction in lipid and DNA oxidation products from healthy humans supplemented with T3 [61].

Finally, the neuroprotection afforded by T3 has been meticulously characterized by studies from Sen's laboratory. Beginning with neuronal cell lines and then into whole animal models, this research has provided the best mechanistic evaluative effort to determine why T3 (especially  $\alpha$ -T3) are neuroprotective at nanomolar concentrations in cells and far more potent than TH [62–64]. This neuroprotection may explain results from a recently published rat study in which early feeding of T3 improved cognitive function [65]. Other animal models of neurodegeneration (stroke) have reported significant neuroprotection by  $\alpha$ -T3 [66,67]. The clinical benefits of T3 and green tea extract supplementation in familial dystonia, a neurodegenerative, auto-recessive genetic disorder associated with reduced brain dopamine and norepinephrine have been demonstrated in humans [68,69]. Overall, enrichment of brain T3 concentrations, T3's *in vivo* antioxidant effects, and significant neuroprotective properties suggest a hypothetical protective mechanism for its inclusion as a complementary nutritional component to the treatment regimen of children with NDD.

Several cellular mechanisms may account for neuroprotection by T3-rich vitamin E. Here vitamin E, like  $\omega$ -3 fatty acids, can regulate many genes, including those associated with hormones, cell viability, neurotransmission, and detoxification of  $\beta$  amyloid plaques [70]. Cellular inhibitory targets of T3 include protein kinase C, a regulatory protein involved in learning and memory [71], 12-lipoxygenase [62], and NF- $\kappa$ B [72] and tyrosine kinases, such as c-Src [64]. Vitamin E also inhibits 5-lipoxygenase and leukotriene B<sub>4</sub> biosynthesis in human cells [73]. Targeting modulation of eicosanoids is worthwhile as proinflammatory eicosanoids and oxidative stress have been reported in autistic children [74]. Indeed, this immunomodulation has been shown in clinical studies with vitamin E, alone or in combination with  $\omega$ -3 fatty acids, in humans in some studies [75–77], but not others [78]. Future experimental and clinical trials should be conducted to determine if T3-rich vitamin E provides immunomodulation in children with NDD.

## Conclusion

Although there are a number of excellent reviews evaluating the potential benefits of  $\omega$ -3 fatty acids in childhood NDD, this study also provides a scientific rationale for inclusion of T3-rich vitamin E as an additional nutritional modifying agent for these children. This rationale, depicted in Figure 3, along with the SECS criteria [10] provides a biochemical and clinical framework for pursuing clinical trials evaluating this combination as a complementary therapeutic option for children with NDD.

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