Long-Chain Polyunsaturated Fatty Acids in Childhood Developmental and Psychiatric Disorders

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ABSTRACT: Both omega-3 and omega-6 long-chain PUFA (LC-PUFA) are crucial to brain development and function, but omega-3 LC-PUFA in particular are often lacking in modern diets in developed countries. Increasing evidence, reviewed here, indicates that LC-PUFA deficiencies or imbalances are associated with childhood developmental and psychiatric disorders including ADHD, dyslexia, dyspraxia, and autistic spectrum disorders. These conditions show a high clinical overlap and run in the same families, as well as showing associations with various adult psychiatric disorders in which FA abnormalities are already implicated, such as depression, other mood disorders, and schizophrenia. Preliminary evidence from controlled trials also suggests that dietary supplementation with LC-PUFA might help in the management of these kinds of childhood behavioral and learning difficulties. Treatment with omega-3 FA appears most promising, but the few small studies published to date have involved different populations, study designs, treatments, and outcome measures. Large-scale studies are now needed to confirm the benefits reported. Further research is also required to assess the durability of such treatment effects, to determine optimal treatment compositions and dosages, and to develop reliable ways of identifying those individuals most likely to benefit from this kind of treatment. Childhood developmental and psychiatric disorders clearly reflect multifactorial influences, but the study of LC-PUFA and their metabolism could offer important new approaches to their early identification and management. Heterogeneity and comorbidity are such, however, that a focus on specific traits or symptoms may prove more fruitful than an exclusive reliance on current diagnostic categories.

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Increasing evidence indicates that disturbances of FA and phospholipid metabolism can play a part in a wide range of psychiatric, neurological, and developmental disorders in adults (1). In recent years it has also become clear that the same factors have a role to play in many childhood neurodevelopmental and psychiatric disorders (2). The latest evidence for this proposal, reviewed here, indicates that a better understanding of the role of long-chain PUFA (LC-PUFA) in these conditions could offer important new approaches to their identification and management.

ADHD, DYSLEXIA, DYSPRAXIA, AND AUTISTIC SPECTRUM DISORDERS

The most common developmental and psychiatric disorders of childhood include attention-deficit/hyperactivity disorder (ADHD), dyslexia, dyspraxia, and autistic spectrum disorders, which between them affect 10–20% of the school-age population. Each is defined by a different and relatively specific pattern of difficulties in behavior and/or learning. Thus in ADHD, the core features involve attentional problems and/or hyperactive-impulsive behaviors; in dyslexia, specific difficulties with reading and writing; in dyspraxia or developmental coordination disorder (DCD), specific weaknesses in the planning and coordination of actions; and in the autistic spectrum, impaired social and communication skills. In practice, however, the overlaps between these conditions are high, and their boundaries with normal variation in behavioral and cognitive function are not at all clear-cut (3–5). "Pure" cases are the exception, not the rule, and within each category there is substantial heterogeneity.

Many features associated with ADHD, dyslexia, dyspraxia, and autistic spectrum disorders are consistent with deficiencies or imbalances in omega-3 and/or omega-6 FA, as discussed in more detail elsewhere (6,7). These include the excess of males affected, slightly increased tendencies for pregnancy and birth complications and minor physical anomalies, and an increased frequency of atopic or autoimmune disorders in affected individuals and their relatives. FA abnormalities could also help to account for some of the key cognitive and behavioral features of these conditions, such as anomalous visual, motor, attentional, or language processing, as well as associated difficulties with mood, digestion, temperature regulation, and sleep.

These developmental conditions all tend to cluster within families, and they also show familial and other associations with certain psychiatric disorders including depression and bipolar disorder as well as schizophrenia spectrum and personality disorders (8–11). This and other evidence points to some common genetic factors in the predisposition to all of these conditions, which may include constitutional anomalies of FA and phospholipid metabolism (12).

THE IMPORTANCE OF LC-PUFA IN BRAIN DEVELOPMENT AND FUNCTION

Omega-3 and omega-6 FA are crucial for normal brain structure

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Abbreviations: AA, arachidonic acid; ADHD, attention deficit/hyperactivity disorder; ALA, α-linolenic acid; DCD, developmental coordination disorder; DGLA, di-homo-γ-linolenic acid; DSM-IV, Diagnostic and Statistical Manual of the American Psychiatric Association, Version IV; GLA, γ-linolenic acid; LA, linoleic acid; LC-PUFA, long-chain polyunsaturated fatty acids; PLA_2, phospholipase A_2; PPAR, peroxisome proliferator-activated receptor; RBC, red blood cell; RCT, randomized controlled trial.

and function, but must be derived from dietary sources. Four LC-PUFA are particularly important to the brain: the omega-6 FA arachidonic acid (AA) and dihomo-γ-linolenic acid (DGLA) and the omega-3 FA EPA and DHA. If not provided directly by the diet, these LC-PUFA must be manufactured *via* desaturation and elongation processes from linoleic acid (LA) in the case of omega-6, or α-linolenic acid (ALA) in the case of omega-3.

Structurally, AA and DHA are key components of neuronal membranes, making up 15–20% of the brain's dry mass and more than 30% of the retina. In early life, both omega-3 and omega-6 LC-PUFA are critical for supporting brain growth and maturation. During prenatal development, adequate supplies are so essential that the placenta doubles the levels circulating in maternal plasma (13), and severe deficits may have permanent effects if they occur during critical periods of early development. AA is crucial to brain growth, and mild deficiencies are associated with low birth weight and reduced head circumference. It also plays a key role in the cellular processes underlying learning and memory. DHA is particularly concentrated in highly active membranes such as synapses and photoreceptors, and adequate supplies are essential for normal visual and cognitive development (14,15). Pre-formed LC-PUFA are found naturally in breast milk, and although some controlled studies have shown advantages to both visual and cognitive development from their addition to infant formula (16), it is not yet clear whether the established benefits of such supplementation for preterm infants may also extend to well-nourished term infants (17).

Throughout life, adequate supplies of LC-PUFA remain crucial for optimal brain function. They increase the fluidity of neuronal membranes, essential for efficient signal transduction, and some act as second messengers in chemical neurotransmitter systems as well as contributing to many other aspects of cell signalling (18) Functionally, three LC-PUFA (DGLA, AA, and EPA) are particularly important as substrates for the eicosanoids—highly bioactive hormone-like substances including prostaglandins, leukotrienes, and thromboxanes. These derivatives play key roles in regulating blood flow and endocrine and immune functions and can modulate ion channels, neurotransmitter uptake, synaptic transmission, apoptosis, and many other biological processes.

An adequate and appropriately balanced supply of LC-PUFA is thus required for normal brain function, both during early development and throughout life. Unfortunately, there are many possible reasons why their availability may be less than optimal, particularly in the case of omega-3 FA.

POSSIBLE REASONS FOR FUNCTIONAL DEFICIENCIES OR IMBALANCES IN LC-PUFA

First, these FA are scarce in many modern diets, especially those in which highly processed foods predominate. This particularly applies to the omega-3 LC-PUFA most important for the brain (EPA and DHA), which are found in appreciable quantities only in fish and seafood. Their precursor, ALA, is found in green vegetables and some nuts and seeds, but its conversion to EPA and DHA is limited, as discussed further below. Omega-6 fats are much more plentiful, because most vegetable oils are rich in LA, and AA is provided directly by meat and dairy products. Overall, the last century has seen dramatic increases in the ratios of omega-6 to omega-3 in average Western-type diets, from approximately 3:1 to more than 20:1 in some cases (19). Gene transfer studies have recently provided powerful evidence that the earlier ratios were much closer to the optimum for healthy human cells (20), and this relative disappearance of omega-3 FA from the diet has already been explicitly linked with increased rates of many disorders of both physical and mental health, including cardiovascular disease, immune disorders, depression, and schizophrenia (19,21–23). Similar effects seem likely with respect to childhood developmental and psychiatric disorders.

Second, there may be difficulties in the synthesis of LC-PUFA from LA or ALA. *In vivo* studies indicate that this conversion process is not very efficient in humans (24,25), but it can also be affected by diet and lifestyle as well as constitutional factors. Males appear particularly vulnerable to LC-PUFA deficiency, as testosterone can impair LC-PUFA synthesis, whereas estrogen helps to protect these FA from breakdown (26,27). Some *in vivo* synthesis of DHA from ALA was observed in adult females (28), but none was detectable in adult males studied using the same methodology (29). These sex differences are interesting in view of the excess of males affected by most of the developmental and psychiatric disorders considered here. LC-PUFA synthesis may also be impaired in atopic conditions such as eczema (30), which are commonly associated with ADHD, dyslexia, autism, and related conditions. From these and other observations, constitutional inefficiencies in LC-PUFA synthesis were explicitly proposed in the first study implicating FA abnormalities in ADHD (31).

Constitutional factors affecting other aspects of FA metabolism may also reduce the availability of LC-PUFA. FA are constantly replaced and recycled during the normal turnover and remodeling of cell membranes and in the chemical cascades triggered by normal cell signalling processes. Phospholipase A_2 (PLA_2) enzymes cleave highly unsaturated FA from the *sn*-2 position of membrane phospholipids, creating FFA and lyso-phospholipids that are highly vulnerable to oxidation and require rapid recycling via at least two further enzyme steps. A huge number of other enzymes are involved in the transport and utilization of FA in the brain and body. Individual differences in their efficiency will have implications for optimal dietary requirements for LC-PUFA, and genetic influences on them may contribute to the risks for various developmental and psychiatric disorders (12).

A ROLE FOR LC-PUFA IN CURRENT THEORIES OF CHILDHOOD NEURODEVELOPMENTAL AND PSYCHIATRIC DISORDERS

The etiologies of ADHD, dyslexia, autism, and related disorders are obviously highly complex and multifactorial. Furthermore, LC-PUFA have such profound and widespread influences on brain development and function that their potential roles in

these conditions are innumerable. In current theories of these neurodevelopmental disorders, however, a few themes seem particularly relevant to possible mechanisms by which FA deficiencies or imbalances could play a contributory role.

Immune function. Many aspects of normal brain development and plasticity are influenced by the immune system (32), and abnormal immune reactivity is increasingly implicated in a wide range of neurodevelopmental and psychiatric disorders (33–37) Imbalances in LC-PUFA will give rise to imbalances in eicosanoid production, and although the relative effects of omega-3 and omega-6 FA on immune function are complex (38), derivatives of AA and EPA generally have opposing actions such that a relative lack of omega-3 increases tendencies toward inflammation and autoimmune reactivity via these and other mechanisms (39).

The minor neuroanatomical abnormalities reported in dyslexic brains postmortem are consistent with inflammatory processes that could plausibly reflect low dietary omega-3 during early development (40). Similarly, some of the visual processing deficits associated with dyslexia are thought to reflect autoimmune influences *in utero* (41). However, functionally inadequate levels of DHA at any developmental stage could play a part, given the crucial importance of this omega-3 FA for visual function, and whether visual deficits in dyslexia may respond to treatment with omega-3 LC-PUFA is the subject of ongoing studies. In addition to its unique role in visual signal transduction (42), DHA also gives rise to derivatives that have anti-inflammatory properties (43,44). These recent findings invite further exploration of the relative contributions of EPA and DHA to immune system changes following LC-PUFA administration, although preliminary evidence suggests that EPA may be more effective in the treatment of neurodevelopmental and psychiatric disorders, as discussed later.

Gut–brain interactions. The gut is a key interface in psychoneuroimmunological reactions—the highly complex interactions between the immune system and the brain, and digestive disorders are highly prevalent in children with neurodevelopmental disorders, especially within the autistic spectrum. In early life, dietary LC-PUFA are important to the establishment and maintenance of healthy gut flora and can influence Th1 and Th2 programming by gut-associated lymphoid tissues, with consequences for autoimmune or allergic responses (45). Relative omega-3 deficiencies may predispose a person to gut inflammation and associated increases in membrane permeability in a variety of ways (46), with negative effects on nutrient absorption and detoxification processes. The potential implications of immune–gut disturbances of this kind are widespread, and include deleterious effects on brain function.

Neurotransmitter function. The limitations of simplistic neurotransmitter-imbalance models of psychiatric illness have long been apparent, but the many ways in which FA and their metabolism can affect the functioning of conventional neurotransmitter systems—and the implications of this for many disorders of mental health and development—are only just starting to be fully appreciated (1,21). These also relate to the issues already mentioned, because many substances regarded primarily as neurotransmitters also play crucial signaling roles in the gut. Furthermore, pro-inflammatory cytokines have been shown to alter the function of monoamine neurotransmitters implicated in stress, sleep disorders, and depression (47,48).

Omega-3 supplementation can modulate the adrenal activation induced by mental stress (49), and dietary omega-3 FA are known to affect serotonergic function, which may help to explain their beneficial effects as reported in controlled trials of depression (50–52) and in preventing or reducing hostility and aggression (53,54). These clinical features are commonly associated with the childhood disorders considered here, raising the possibility that LC-PUFA could also help in the management of these conditions.

ADHD is routinely treated using stimulant medications that increase the availability of dopamine, a fact reflected in all pharmacological theories of this condition. It is thus of interest that chronic omega-3 deficiency reduces dopamine (and its binding to D_2 receptors) in the frontal cortex and is associated with comparable attentional and behavioral dysfunction in animal studies (55,56). Recent evidence from such studies indicates that some effects of early omega-3 deficiency on dopaminergic systems may be more amenable to subsequent dietary interventions than others (57), but whether ADHD symptoms in children can be reduced by LC-PUFA treatment still requires further exploration in clinical trials, as discussed later.

EVIDENCE FOR FA ABNORMALITIES IN CHILDHOOD DEVELOPMENTAL AND PSYCHIATRIC DISORDERS

Physical signs consistent with FA deficiency—such as excessive thirst; frequent urination; rough, dull, or dry hair and skin; and soft or brittle nails—have been repeatedly linked with ADHD, dyslexia, and autistic spectrum disorders (31,58–63). These kinds of physical symptoms can obviously have other causes, but their association with these neurodevelopmental disorders merits further investigation.

Reduced blood concentrations of LC-PUFA in ADHD children compared with controls have been found in several studies (62–66). The precise pattern of results has varied, but reductions of AA as well as DHA have usually been apparent, and plasma concentrations appear to show the most consistent findings. One recent study still found reduced plasma LC-PUFA in ADHD children despite significantly elevated concentrations of the same FA in red cell membranes (67). Relationships between blood biochemical and behavioral or health measures have also been explored in some studies. In 16 boys with ADHD, behavior problems were inversely correlated with γ-linolenic acid (GLA), but not its precursor LA, in serum TG (68), which was interpreted as reflecting a possible bottleneck in this conversion pathway. In a larger study of 96 ADHD and control boys, behavioral and learning problems were greater in those with low vs. high plasma phospholipid concentrations of omega-3 FA, irrespective of clinical diagnosis; but no such association was found for low and high omega-6 FA groups (65).

In autistic spectrum subjects LC-PUFA abnormalities have been reported in both plasma (69) and red blood cell (RBC) membranes (59,60). Findings include particular reductions in omega-3 LC-PUFA, an elevated AA/EPA ratio and an apparent increased susceptibility to the breakdown of membrane FA, possibly reflecting increased oxidative stress (70).

In dyslexia, blood biochemical studies to date are few, but include one early case report of FA deficiency in a dyslexic child (71) and the finding of elevated levels of a Type IV PLA_2 enzyme in RBC membranes of dyslexic adults relative to controls (72). New studies have also yielded interesting preliminary results. Omega-3 concentrations in RBC polar lipids were directly correlated with reading ability in both dyslexic and nondyslexic adults, although they did not differ significantly between the two groups (73). Poor working memory performance—a hallmark of dyslexia—was associated with low omega-3 status only in dyslexic adults, not in controls; and the same was true of schizotypal personality traits involving attentional dysfunction (74).

Although these kinds of studies broadly support the proposal that LC-PUFA may play a part in these childhood developmental and psychiatric disorders, the interpretation of blood biochemical measures remains difficult. They reflect complex interactions between influences of diet and other environmental factors with constitutional aspects of FA metabolism, and not enough is yet known about normal variability in LC-PUFA in compartments such as RBC vs. plasma, or TG vs. phospholipid fractions. Further investigations of the clinical significance of these kinds of measures are needed, ideally using samples drawn from the general community.

RANDOMIZED CONTROLLED TRIALS OF FA TREATMENT IN ADHD, DYSLEXIA, AND RELATED CONDITIONS

Intervention studies provide the most direct evidence that FA can play a role in developmental and psychiatric disorders of childhood. Anecdotal evidence, case reports, and open studies all suggest possible benefits from FA treatment in these conditions (71,75,76), but randomized controlled trials (RCT) are essential to demonstrate causality. Published studies of this kind remain few, although others are in progress. Only an overview summary can be provided here, but a recent review provides further details (77).

Two of the earliest RCT assessed the effects of evening primrose oil (providing the omega-6 FA GLA) in hyperactive or ADHD children (78,79). Unfortunately, the study designs were not optimal in either case, involving treatment periods of only one month as well as potential confounds from the use of full-treatment crossover. Few benefits from such supplementation were apparent from these trials, although some positive trends were noted.

Since then, emphasis has shifted toward omega-3 FA, but two studies have shown no benefits from supplementation with DHA alone. In the first of these (80), 63 U.S. children aged 6–12 yr with a formal DSM-IV diagnosis of ADHD were randomized to treatment with either 345 mg/d of pure algal-source DHA or placebo for 4 mon in addition to maintenance stimulant medication. Outcome measures included scores on computer-presented tests of inattention and impulsivity as well as clinical and parent ratings of ADHD symptoms. Compared with the placebo, active treatment significantly increased DHA in plasma phospholipids, but no group differences were found for any behavioral outcomes. The second such RCT involved 40 Japanese children aged 6–12 yr attending a summer camp for their ADHD-type difficulties (81). They received either foods fortified with DHA (at a dosage of approximately 0.5 g/d) or indistinguishable control foods for 2 mon. A wide range of measures was used pre-and post-treatment, but the only significant difference between treatment groups involved greater improvements over time on visual and auditory memory tests for those on placebo.

In contrast to these negative results for DHA, two other studies have shown some reduction in ADHD symptoms in children treated with combined omega-3/omega-6 supplements. One involved 50 ADHD-type children, preselected for physical signs consistent with FA deficiency and treated for 4 months with a supplement containing fish oil and evening primrose oil in a 4:1 ratio (providing 480 mg DHA, 80 mg EPA, 96 mg GLA, 40 mg AA, and 24 mg alpha-tocopheryl acetate daily) or an olive oil placebo (82). Both groups showed improvements, but significant benefits for active treatment over placebo were found for 2 of 16 outcomes—parent-rated conduct problems and teacher-rated attentional difficulties. In addition, oppositional defiant behavior dropped from clinical to subclinical levels in significantly more children receiving active treatment.

The other positive study used very similar treatments but involved children with a primary diagnosis of dyslexia who were selected for above-average ADHD-related symptoms (83). After 12 wk of supplementation (providing 480 mg DHA, 186 mg EPA, 96 mg GLA, 42 mg AA, and 60 IU vitamin E as DL-α tocopherol per day), scores for anxiety, attentional difficulties, and general behavior problems were significantly lower for the 15 children on active treatment than the 14 on the olive oil placebo. In a 12-wk follow-up stage involving one-way treatment crossover, similar improvements in ADHD-related symptoms were then seen in the placebo group when they switched to active treatment (84).

These contrasting results still require elucidation *via* further research. Two particular issues worth considering here, however, include the populations studied and the nature of the treatments used.

Populations studied. Research into the underlying biology of ADHD, dyslexia, and related conditions is complicated by the descriptive and categorical nature of these diagnoses, as there is always substantial heterogeneity within such clinically defined populations. In both of the negative studies using DHA, participants were selected using purely behavioral criteria rather than from a biochemical perspective. The U.S. study (80) involved full psychiatric evaluation and included only children formally diagnosed with "pure" DSM-

IV ADHD. Given the high comorbidity within ADHD, this would rule out a large proportion of children otherwise eligible for this diagnosis and might even equate to "throwing out the baby with the bathwater." In adults, omega-3 FA have already shown promise in the treatment of unipolar depression (50–52), bipolar disorder (85), and borderline personality disorder, (54) so excluding those ADHD children with comorbid difficulties of this kind might well eliminate those most likely to benefit from this type of treatment. Many children receiving the ADHD diagnosis have comorbid anxiety or mood disorders. Furthermore, stimulant medications appear to be ineffective in up to 70% of ADHD children with this profile (86–88), and their negative side effects more likely (89). Given the evidence from studies of adults with mood-related disorders, omega-3 treatment trials seem well warranted in these subsets of ADHD children, as well as in children with a primary diagnosis of depression.

In the Japanese study showing negative results for DHA-fortified foods (81), children were again selected for ADHD, although formal diagnostic information was limited. Biochemical measures were not available to assess FA status, but background diet might have been a factor given that Japanese diets are traditionally fairly rich in omega-3.

By contrast, the U.S. study showing some benefits from LC-PUFA (82) took a biochemical perspective, in that subjects were preselected for physical signs consistent with FA deficiency that had previously been found to relate to blood FA concentrations (63). Formal psychiatric diagnoses of ADHD were not used, although all children were under clinical care for this condition. Instead, recruitment was by advertisement, so that comorbidity probably reflected the usual high levels found in community samples. The other positive study (83) involved dyslexic children who were selected for above-average scores on dimensional measures of ADHD-related symptoms. Similar findings have now emerged from a larger, but as yet unpublished, trial of children with a primary diagnosis of dyspraxia/DCD (see Ref. 77), although biochemical measures were not included in either of these studies.

Preliminary evidence therefore suggests that treatment with LC-PUFA can ameliorate ADHD-related symptoms in at least some groups of children who show these kinds of behavioral and learning difficulties. Careful consideration of comorbidity issues seems worthwhile in further studies, although the inclusion of biochemical measures of FA status would also be an obvious advantage.

Composition of FA treatments. The optimal composition of LC-PUFA treatments also requires further investigation. There is no convincing evidence that omega-6 FA alone are of benefit in these conditions, although this has only been explored in the first small studies using evening primrose oil. With respect to omega-3, two studies found DHA ineffective in reducing ADHD symptoms (80,81), and two others found some advantages over placebo for supplements containing both EPA and DHA (as well as some omega-6) (82,83). Evidence from several RCT involving adult psychiatric patients suggests that EPA may be more effective than DHA in the treatment of functional disturbances of attention, cognition, or mood. Thus, DHA has been found ineffective in treating both depression (90) and schizophrenia (91), whereas pure EPA has shown significant benefits in these conditions (50,51,92).

Findings to date therefore suggest that EPA may be more effective than DHA in the conditions discussed here, which may seem counterintuitive given that DHA is undeniably more important than EPA in the structure of neuronal membranes. EPA nonetheless appears to play many key functional roles in the brain. Its eicosanoid derivatives are key regulators of immune, endocrine, and cardiovascular functions, and direct actions of EPA on cyclo-oxygenases, lipoxygenases, phospholipases, acylating systems, ion channels, mitochondria, and peroxisome proliferator-activated receptors (PPAR) are the focus of current investigations across many different fields of study. No studies have yet shown any benefits from pure DHA in developmental or psychiatric disorders, but direct comparisons of EPA and DHA—and of treatments containing these in different proportions—are needed to establish with any certainty their relative merits in the treatment of these conditions.

SUMMARY AND CONCLUSIONS

The childhood developmental and psychiatric disorders considered here are complex, multidimensional syndromes with considerable overlap at the individual and familial levels. The evidence reviewed here suggests that they share some common biological risk factors, and that these may include abnormalities of FA metabolism that increase dietary requirements for these essential nutrients.

Findings from controlled trials suggest that LC-PUFA supplements may be of some value in the management of these conditions. Modest benefits in reducing ADHD-related symptoms have been observed in two studies using combined omega-3/omega-6 FA from fish oil and evening primrose oil, but other studies using GLA or DHA alone have been negative. Together with similar evidence from studies of adult psychiatric disorders, these findings raise the possibility that the omega-3 FA EPA may be the most effective component of FA treatments aimed at improving behavior, learning, and mood. Larger studies involving direct comparisons of different treatments are needed to resolve these issues

In conclusion, a biochemical/nutritional approach focusing on FA and their metabolism offers considerable promise in identifying at least some factors contributing to childhood developmental and psychiatric disorders, and could lead to better methods for early identification and treatment of these conditions. It is argued here, however, that an exclusive focus on current diagnostic categories may be unhelpful given the substantial heterogeneity and comorbidity involved. Dimensional measures of specific traits and symptoms may prove more useful in identifying those individuals most likely to benefit from this approach.

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