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Vitamin D and the omega-3 fatty acids control serotonin synthesis and action, part 2: relevance for ADHD, bipolar, schizophrenia, and impulsive behavior

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ABSTRACT **Serotonin regulates a wide variety of brain functions and behaviors. Here, we synthesize previous findings that serotonin regulates executive function, sensory gating, and social behavior and that attention deficit hyperactivity disorder, bipolar disorder, schizophrenia, and impulsive behavior all share in common defects in these functions. It has remained unclear why supplementation with omega-3 fatty acids and vitamin D improve cognitive function and behavior in these brain disorders. Here, we propose mechanisms by which serotonin synthesis, release, and function in the brain are modulated by vitamin D and the 2 marine omega-3 fatty acids, eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA). Brain serotonin is synthesized from tryptophan by tryptophan hydroxylase 2, which is transcriptionally activated by vitamin D hormone. Inadequate levels of vitamin D (~70% of the population) and omega-3 fatty acids are common, suggesting that brain serotonin synthesis is not optimal. We propose mechanisms by which EPA increases serotonin release from presynaptic neurons by reducing E_2 series prostaglandins and DHA influences serotonin receptor action by increasing cell membrane fluidity in postsynaptic neurons. We propose a model whereby insufficient levels of vitamin D, EPA, or DHA, in combination with genetic factors and at key periods during development, would lead to dysfunctional serotonin activation and function and may be one underlying mechanism that contributes to neuropsychiatric disorders and depression. This model suggests that optimizing vitamin D and marine omega-3 fatty acid intake may help prevent and modulate the severity of brain dysfunction.—Patrick, R. P., Ames, B. N. Vitamin D and the omega-3 fatty acids control serotonin synthesis and action, part 2: relevance for ADHD, bipolar, schizophrenia, and impulsive behavior. *FASEB J.* 29, 000–000 (2015). www.fasebj.org**

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"The rapid progress true science now makes, occasions my regretting sometimes that I was born too soon. It is impossible to imagine the height to which may be carried, in a thousand years, the power of man over matter. We may, perhaps, deprive large masses of their gravity, and give them absolute levity, for the sake of easy transport. Agriculture may diminish its labor and double its produce: all diseases may by sure means be prevented or cured, (not excepting even that of old age,) and our lives lengthened at pleasure, even beyond the antediluvian standard. Oh that moral science were in as fair a way of improvement, that men would cease to be wolves to one another, and that human beings would at length learn what they now improperly call humanity."

– Benjamin Franklin letter to Joseph Priestley, 1780

SEROTONIN PLAYS A CRITICAL role in brain function as a neurotransmitter, hormone, and brain morphogen (1). Serotonin is concentrated in discrete brain regions known to regulate social cognition and decision-making that have been collectively called "the social brain" (2–4). There is an abundance of evidence linking serotonin to social behavior (5, 6). For example, polymorphisms in the serotonin transporter gene have been linked to social behavioral defects including aggression, impulsivity, anxiety, psychopathology, and personality disorder (7–11). Experimentally lowering brain serotonin levels in normal people has a wide range of behavioral consequences: impulsive behavior, impaired learning and memory, poor long-term planning, inability to resist short-term gratification, and social behavioral deficits characterized by impulse aggression or lack of altruism (5, 12–14). Because social behavior is disrupted in many brain disorders, such as autism spectrum disorder (ASD), attention deficit hyperactivity disorder (ADHD), bipolar disorder, schizophrenia, impulsive behavior disorder, depression, and anxiety, understanding the biologic mechanisms that regulate the serotonin pathway are important for understanding how social cognition and decision-making become dysfunctional in these disorders.

Despite the wealth of data that links serotonin to social behavior, specific factors that make an individual more susceptible to social-cognitive dysfunction and mental

Abbreviations: 5-HIAA, 5-hydroxy-indole acetic acid; 5-HT, serotonin; 25(OH)D_3, 25-hydroxyvitamin D; ADHD, attention deficit hyperactivity disorder; ASD, autism spectrum disorders; DHA, docosahexaenoic acid; EPA, eicosapentaenoic acid; *IDO*, indoleamine 2,3-dioxygenase; TPH, tryptophan hydroxylase; *TPH1*, tryptophan hydroxylase 1; *TPH2*, tryptophan hydroxylase 2; VDRE, vitamin D response element

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illness remain unclear. One challenge in this field of research is the complexity of interactions that manifest as a given disorder. Neuropsychiatric disorders are multifactorial and are likely influenced by a complex interaction between genetics, nutrition, and environment (15). There has been significant progress in the identification of gene variations associated with psychiatric disorders and some have shared genetic etiology (16). What is less understood is how nutritional deficiencies may interact with genetic pathways, such as the serotonin pathway, that are important for brain development, social cognition, and decision-making, and how the gene-environment interactions may trigger mental illness. Cognitive functioning involves billions of neurons working with numerous biochemical pathways and associated enzymes. Many of these enzymes require micronutrients, essential vitamins, and minerals as cofactors for optimal function. Thus, one expects that suboptimal function caused by micronutrient inadequacies could adversely affect the functions of proteins and enzymes involved in brain function. Multiple factors including micronutrient inadequacies, exercise, inflammation, and stress have all been shown to influence the serotonin pathway, as we will discuss here, and, consequently, affect social behavior (schematic representation of serotonin pathway illustrated in **Fig. 1**) (17–21). In a previous paper (part 1 of this series), we provided evidence for a biologic mechanism by which vitamin D hormone regulates serotonin synthesis in a tissue-specific manner and how aberrant serotonin production during fetal and neonatal development may play a central causal role in ASD (22).

Here, we assemble evidence from the literature that serotonin regulates executive function, impulsivity, sensory gating, and social behavior and propose that ASD, ADHD, bipolar disorder, schizophrenia, and impulsive behavior all share defects in these functions because of dysfunction in the serotonin pathway. We build on our previous findings on how vitamin D hormone is a key regulator of brain serotonin synthesis through tryptophan hydroxylase 2 (*TPH2*), which contains a vitamin D response element (VDRE) consistent with activation and how this relates to psychiatric disorders (22). We propose mechanisms by which the marine omega-3 fatty acids eicosapentaenoic acid (EPA) increases serotonin release from presynaptic neurons by reducing E2 series prostaglandins and docosahexaenoic acid (DHA) influences serotonin action by increasing membrane fluidity and thus serotonin receptor accessibility in postsynaptic neurons. Because vitamin D insufficiency and low dietary intake of omega-3 fatty acids are very common, we propose that suboptimal intake of these micronutrients contribute to dysfunction of the serotonin pathway, and, in combination with genetic factors, exacerbate dysfunction in the serotonin system, resulting in defects in executive function, impulse control, sensory gating, and prosocial behavior, and precipitate neuropsychiatric disorders. These brain disorders have a higher male incidence, which we suggest is because of a protective effect of estrogen, resulting in an increase in brain serotonin synthesis in females. Finally, we suggest that supplementation with vitamin D and omega-3 fatty acids may aid in the prevention of mental illness and/or help modulate the severity of brain dysfunction.

ROLE OF SEROTONIN IN NEUROPSYCHIATRIC ILLNESS

Serotonin regulates executive function and sensory gating

Executive function is modulated by serotonin, and it is essential for planning and decision-making; the latter of these actions involves weighing the expected gains, losses, and probabilities of each of these outcomes (19, 23). Brain serotonin levels have been experimentally lowered by administering branch-chain amino acids, which strongly outcompete tryptophan for transport across the blood-brain barrier and cause serotonin levels to plummet (hereafter referred to as acute tryptophan depletion) (23). Acute tryptophan depletion in healthy volunteers, which lowers brain serotonin levels, compromises the decision-making process by altering the ability to distinguish the magnitude of differences between immediate *versus*, long-term rewards (19). Tryptophan depletion also increases the tendency to choose the less probable outcome, similarly to what happens in amphetamine drug users and individuals with damage to the prefrontal cortex, which compromises executive function (24). Another integral part of decision-making is the ability to abstain from short-term gratification to benefit in the long term. Depleting serotonin in normal individuals shifts their behavior toward lack of impulse control and short-term gratification at the expense of long-term benefits (13, 25–27). Tryptophan depletion results in enhanced activity in the ventral striatum, which is the part of the brain associated with short-term decision-making (28). In contrast, supplementation with tryptophan causes activation of the dorsal striatum, which is responsible for long-term decision-making (28). Thus, it appears that decision-making and impulsive choices are both controlled by serotonin.

Sensory gating, which is the ability of the brain to filter out extraneous sensory inputs, also depends on serotonin levels. Defects in sensory gating cause a sensory overload of irrelevant information resulting in cognitive fragmentation, which shares comorbidity with numerous psychopathological disorders (21–26). Acute tryptophan depletion in normal individuals results in impaired sensory gating, thus suggesting that serotonin plays an important role in this process (29, 30). Defects in sensory gating may also affect executive function and decision-making. In general, the overall data support the concept that low serotonin levels lead to impairments in executive function and sensory gating.

Serotonin regulates social behavior and impulsivity

Serotonin plays an important role in inhibiting impulsive aggression toward self, including suicide, and aggression toward others (5, 31). Depleting brain serotonin levels in normal individuals results in a shift away from cooperative behavior in favor of short-term gain and results in antisocial behavior, increased uncontrolled aggressive behavior, feelings of anger, quarrelsome behavior, and self-injury (5, 20, 32–35). In adolescents with ADHD, depleting brain

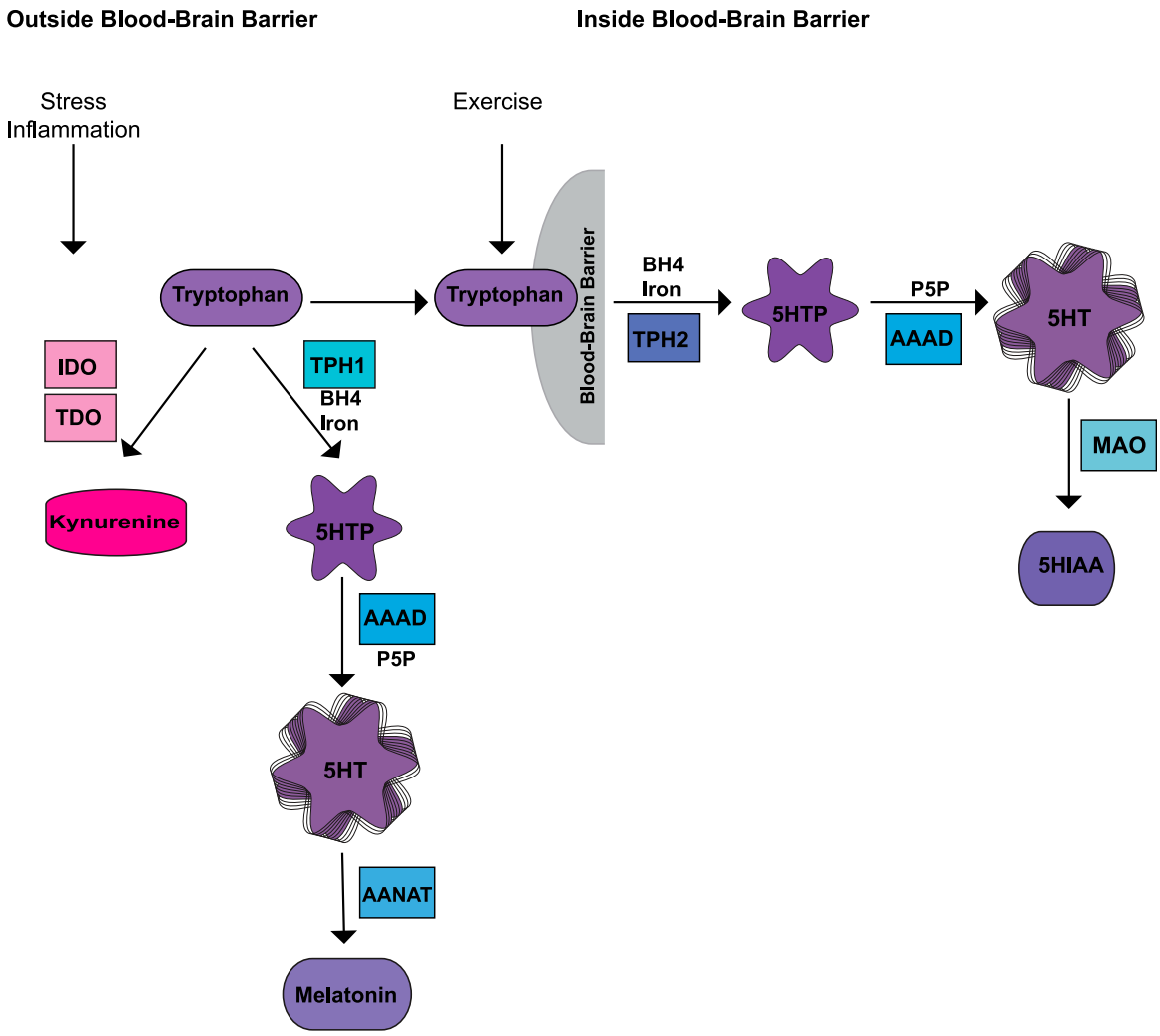

Figure 1. Metabolic pathways of tryptophan. Stress and inflammation activate the enzymes indoleamine 2,3-dioxygenase (IDO) and tryptophan 2,3-dioxygenase (TDO), which metabolize tryptophan to kynurenine and shunt it away from transport into the brain. Alternatively, tryptophan can be metabolized by the enzyme tryptophan hydroxylase 1 (TPH1), which uses tetrahydrobiopterin (BH4) and iron as cofactors, to produce 5-hydroxytryptophan (5HTP). 5HTP is metabolized by the enzyme aromatic L-amino acid decarboxylase (AAAD), which uses pyridoxal 5-phosphate (P5P) as a cofactor, to produce 5HT. 5HT is metabolized by the enzyme *N*-acetyl transferase (AANAT) to produce the sleep hormone, melatonin. To produce serotonin (5HT) in the brain, tryptophan must first be transported across the blood-brain barrier. This transport depends on the ratio of tryptophan to branch-chain amino acids, which strongly outcompete tryptophan for transport across the blood-brain barrier. Exercise alleviates this competition by increasing the uptake of branch-chain amino acids into muscle, thus raising tryptophan availability to the brain. Inside the brain, tryptophan is metabolized by the rate-limiting enzyme, tryptophan hydroxylase 2 (TPH2), to produce 5HTP in the brain. 5HTP is metabolized by AAAD to produce 5HT in the brain. 5HT is metabolized by the enzyme monoamine oxidase (MAO) to produce the inactive serotonin metabolite 5-hydroxyindoleacetic acid (5HIAA).

serotonin levels increased aggressive behavior (36). Depleting brain serotonin levels has also been shown to cause loss of inhibitory behavior against adverse consequences, which is linked to recidivism (5, 12, 14, 33). In contrast, acutely enhancing brain levels of serotonin causes people to become more averse to harming others, suggesting that serotonin may play a role in moral behavior (20). Tryptophan supplementation has been shown to decrease social anxiety and quarrelsome behavior in normal individuals and in irritable individuals and may therefore improve overall social behavior (37–40). Additionally, tryptophan supplementation in young boys with disruptive behavior decreased impulsivity and increased social cooperation (41). Furthermore, tryptophan supplementation in schizophrenics can reduce aggression and the need for antipsychotics (42, 43). These studies support a causal role for serotonin in regulating social behavior.

In nonhuman primates, low brain serotonin also leads to severe aggressive behavior and lack of impulse control (44). In mice, dietary tryptophan depletion increases killing behavior that is ameliorated by boosting brain serotonin levels (45, 46). Mutant mice that have a nonfunctional or deleted *tph2*, and thus have no serotonin synthesis in the brain, display exaggerated aggressive behavior and compulsive behavior compared with control mice (47–49). These data provide evidence that serotonin deficiency in the brain leads to magnified aggression.

Polymorphisms in serotonin-related genes are associated with mental illness

ASD, ADHD, bipolar disorder, schizophrenia, and impulsive behavior disorders have significant overlap because they all exhibit impairments in executive function, sensory gating, and social behavior. These impairments are characterized by a plethora of phenotypes including poor long-term planning skills, impulsivity, poor attention switching, emotional dysregulation, impaired sensory gating, poor social skills, impulse aggression toward self and others, and depression (50–58). Because serotonin plays a key role in regulating many of these executive and behavioral functions, aberrant serotonin signaling is likely to be a unifying underlying cause common to these psychopathologic disorders. Indeed, brain serotonin has been shown to be low in ASD, ADHD, bipolar disorder, schizophrenia, and impulsive behavior disorders (22, 59–61). The concentration of the serotonin metabolite 5-hydroxy-indole acetic acid (5-HIAA) in cerebrospinal fluid is a biomarker for low brain serotonin levels. Low 5-HIAA levels are associated with detrimental behaviors such as aggression, violent suicide, impulsive murder, and recidivism of murder and have also been found in individuals with depression (62–68).

Polymorphisms in the *TPH2* gene and other serotonin-related genes provide additional support that aberrant brain levels of serotonin are associated with increased susceptibility to ASD, ADHD, bipolar disorder, schizophrenia, and impulsive behavior, including aggression toward self and others (22, 69–75). These polymorphisms are also associated with aggression, depression, and anxiety, which are all common psychologic abnormalities in these psychiatric disorders (76–78). Suicide is strongly linked to impulsive behavior and polymorphisms in tryptophan hydroxylase, and other serotonin-related pathways have been linked to increased suicide attempts (79, 80). In a recent study, 58% of suicide attempters were vitamin D deficient, their levels of vitamin D being significantly lower than those in healthy individuals and patients with depression, but without suicidality (81). In line with this, lower duration of daily sunshine has also been linked to higher suicide frequency independent of season (82, 83).

THE ROLE OF VITAMIN D IN NEUROPSYCHIATRIC ILLNESS

Vitamin D regulates serotonin

Vitamin D is first converted to 25-hydroxyvitamin D [25(OH)D_3], which is the major stable circulating form of vitamin D, and then to the biologically active steroid hormone 1,25-dihydroxyvitamin D (84). We recently proposed an underlying mechanism that describes how vitamin D hormone, which appears to control >900 genes, is a key regulator of brain serotonin synthesis through *TPH2,* which contains a VDRE consistent with activation (22, 85). We identified 2 distinct VDREs present in the regulatory regions of both *TPH2* and *TPH1*, the 2 genes responsible for the conversion of tryptophan into serotonin in the brain vs. other tissues, respectively (22). We proposed that the VDREs would respond to vitamin D hormone in an inverse mode, with *TPH2* being transcriptionally activated in the brain and *TPH1* repressed in tissues outside of the blood-brain barrier (22). This proposal was based on evidence that the VDRE sequence alone can determine whether vitamin D hormone will activate or repress gene transcription (86). New biochemical evidence validates our proposal by showing that vitamin D hormone activates *TPH2* expression in cultured neuronal cells (M. Haussler, personal communication, 7/19/2014; see Note added in proof).

Vitamin D sufficiency

The precise blood level of 25(OH)D_3 that is defined as vitamin D deficiency remains somewhat controversial. Based on the classic function of vitamin D, which is to maintain bone homeostasis, vitamin D deficiency has been defined by the Institute of Medicine as 25(OH)D_3 serum concentrations <20 ng/ml (87). The current guidelines for vitamin D sufficiency have been suggested to be >30 ng/ml (87).

According to the U.S. National Health and Nutrition Examination Survey, vitamin D sufficiency (30–60 ng/ml) decreased between 1994 and 2004 from ~60% to 30% in whites, from 10% to 5% in African Americans, and from 24% to 6% in Latinos, indicating that more than half of the US population has insufficient levels of this critical vitamin D hormone (88, 89). Currently, ~70% of adults and 67% of children aged 1–11 y in the United States do not have adequate levels of vitamin D even when fortification and supplementation are considered (89–91). Epidermal synthesis of vitamin D requires the action of UVB radiation emitted from the sun; however, the use of sunscreen and also a high level of melanin, the brown pigment found in skin, block UVB radiation, thus impairing the ability of the skin to synthesize vitamin D (84, 92, 93). In addition, living at Northern latitudes decreases skin exposure to UVB (84). A modest amount of vitamin D can be obtained through dietary sources, such as seafood, which is its relatively richest dietary source (94). Some foods have been fortified with vitamin D, including milk (100 IU per 8 oz) and orange juice (100 IU per 8 oz), but these levels are not sufficient to achieve an adequate vitamin D status of 30 ng/ml. Furthermore, dairy products are a poor choice for fortification for the ~50 million Americans who are lactose intolerant, including 75% of African Americans (95).

Vitamin D may modify severity of brain dysfunction

There may be a very important interaction between genetics and vitamin D hormone that could play a role in modulating the severity of mental illness. Individuals with polymorphisms in serotonin-related genes are already predisposed to dysregulation in the synthesis or metabolism of serotonin; thus, any additional decrease in serotonin synthesis as a consequence of inadequate levels of vitamin D may exacerbates defects in executive function, sensory gating, and impulsive behavior. Low 25(OH)D_3 serum concentrations have been shown to be associated with an elevated risk for ASD, ADHD, bipolar disorder, schizophrenia, antisocial behavior, and impulsive behavior (22, 96–101). There appears to be an interaction between

polymorphisms in serotonin-related genes and season of birth: individuals with bipolar disorder or schizophrenia who also have polymorphisms in the *TPH* gene or the gene that encodes the serotonin transporter have an increased risk of mental illness if they were born in winter/spring months (102). The interaction between vitamin D deficiency and defects in serotonin-related genes has also been demonstrated in mice: mice that already have reduced serotonin synthesis caused by a polymorphism in their *TPH2* gene are very sensitive to vitamin D deficiency in adulthood and as a result have profound defects in cognitive function and behavior when vitamin D is restricted (103, 104). Presumably, these mice have more pronounced defects in behavior because of further dampening of serotonin synthesis as a consequence of vitamin D deficiency. These studies highlight the role that vitamin D hormone plays in modulating severity of brain dysfunction in combination with genetic factors affecting brain serotonin levels.

Timing of vitamin D deficiency may exacerbate brain dysfunction

In addition to genetic factors, the timing of vitamin D deficiency and stage of development in which it occurs affects the severity of executive function, sensory gating, and social behavior dysfunction. Gestational vitamin D deficiency in rats leads to later impairments in latent inhibition (which is related to sensory gating), attention processing, and impulsive behavior (105, 106). Consistent with these results, mutant mice lacking a functional vitamin D receptor have defects in sensory gating and abnormal social behavior, including social neglect and impulsive behavior (107, 108). However, when vitamin D is restricted only during adulthood, the behavioral abnormalities, including impulsive behavior and impaired attention processing, are more subtle than the effects of vitamin D deficiency throughout life (107–109). These subtle effects of vitamin D deficiency during adulthood are in contrast with the more severe behavioral effects observed in mice that are already predisposed to low serotonin synthesis (104). Thus, the severity of behavioral abnormalities in response to low vitamin D are more pronounced when deficiency occurs during development but are also exacerbated by genetic factors that also affect the serotonin system.

Insufficient vitamin D during early development can precipitate social cognition, decision-making, and brain morphology defects that share similarity with many brain disorders. This may in part be because of the important role vitamin D and serotonin both have on the structure and wiring of the brain (110, 111). In rats, gestational vitamin D deficiency leads to a 200% increase in lateral ventricle volume, a slightly lower neocortical width, increased cell proliferation, decreased differentiation, and a decrease in neurotrophic factors (112, 113). In humans, gestational vitamin D deficiency has been shown to cause an increase in neonatal ventricle size by as much as 28% (114). Enlargement of cerebral lateral ventricles is known to be associated with ASD, ADHD, and schizophrenia (115). It is plausible if this aberrant brain morphology is assumed to play a role in the etiology of these brain disorders, perhaps this same ventricular enlargement, when caused by early gestational vitamin D deficiency, may also precipitate those same illnesses in the presence of the correct genetic-environmental background.

There is significant evidence that low vitamin D levels during gestational and neonatal development are a risk factor for schizophrenia and psychosis, in some cases raising the risk by 6-fold (97, 98, 116–119). Furthermore, the absence of vitamin D supplementation during pregnancy is associated with an increased risk of schizophrenia in male children (120). Low vitamin D levels have been associated with an increased risk of psychotic experiences in both childhood and adolescence (121, 122). A meta-analysis found schizophrenia prevalence rates increased significantly with increased latitude; however, lighter skin color, a factor improving vitamin D status, and high intake of fish were both associated with protection against schizophrenia (99). These data suggest that vitamin D may play an important role in shaping the structure of the developing brain and decreasing psychosis and schizophrenia.

Vitamin D supplementation: a simple solution?

Supplementation with vitamin D during early brain development may be able to decrease the risk of neuropsychiatric disorders and supplementation later in life may improve brain dysfunction. This may be partially mediated through the ability of vitamin D to activate *TPH2* and thus increase serotonin synthesis (22) (M. Haussler, personal communication, 7/19/2014). Low levels of vitamin D are common in ASD, ADHD, bipolar disorder, schizophrenia, and impulsive behavior (22, 81, 96, 122–125). For this reason, many individuals at risk or already diagnosed with any of these disorders would benefit by a vitamin D supplement. Indeed, vitamin D supplementation during the first year of life decreased the incidence of schizophrenia by 77% (120). This is particularly relevant because there is a wide range of vitamin D insufficiency among pregnant women (up to 91%) in the United States. This level of insufficiency varies according to which state people live in, perhaps because of differences in sun exposure (126). Approximately 50% of mothers taking prenatal vitamins and their neonates had insufficient levels of vitamin D, whereas supplementation with 4000 IU/d, which is the upper tolerable intake, was safe and most effective in achieving adequate vitamin D concentrations without toxicity (127, 128). Vitamin D supplementation has also been shown to improve inattention, hyperactivity, and impulsivity in children and adults with ADHD (129, 130). Given the widespread vitamin D deficiency, particular in those with brain dysfunction, these data suggest that a vitamin D supplement that is 4000 IU may be able to eliminate vitamin D deficiency and help reduce psychiatric disease risk and improve brain function. More clinical studies investigating this will shed light.

Omega-3 FATTY ACIDS REGULATE SEROTONIN FUNCTION

Omega-3 fatty acids affect behavior

Long chain marine omega-3 fatty acids in the brain consist primarily of the C22 *n*-3 DHA with some C20 *n*-3 EPA (131).

Blood concentrations of EPA and DHA have been found to be low in individuals with a wide range of psychiatric illnesses including ASD, ADHD, bipolar disorder, schizophrenia, suicide attempters, and other impulsive behavior; supplementation has been shown to have a beneficial role in modifying the severity of symptoms (22, 132–136). Schizophrenics have significantly lower DHA levels in the orbitolfrontal cortex region of the brain, where serotonin is concentrated, compared with normal individuals (137). Epidemiologic studies suggest that ω-3 deficiency may be a risk factor for bipolar disorders: plasma DHA is significantly decreased in bipolar patients (135). Suicidal ideation is common in individuals with bipolar disorder and depression and has been linked to both low omega-3 and low serotonin in the brain (138, 139). Randomized controlled trials have found that supplementation with several grams of EPA and DHA improved depression, suicidal thoughts, and behaviors (132, 140). Supplementation with omega-3 from fish oil was shown to improve cognitive function, including language skills, concentration, motor skills, schizophrenic symptoms, and aggressive and impulsive behavior (132, 141). Intervention studies have shown that supplementation with omega-3 fatty acids improved aggression, anger, hostility, antisocial behavior, anxiety, and impulsivity in normal school children, juvenile delinquents, adolescents, prison inmate populations, and substance abuse users (142, 143). Although many recent meta-analyses show a clear benefit for omega-3 fatty acids in the treatment of depression, there is some heterogeneity between clinical trials (144–149). Some plausible explanations for inconsistent results include genetic variation, omega-3 fatty acid from diet, and different EPA and DHA doses in various formulations, as EPA appears to play a more important role (150, 151). A large clinical trial measuring omega-3 fatty acid concentrations in red blood cells and testing multiple doses of EPA and DHA compared with placebo should help shed light.

EPA regulates serotonin release

We propose that one important mechanism by which omega-3 fatty acids modulate serotonin function is through regulation of serotonin release in the presynaptic neuron (Fig. 2). Serotonin release is inhibited by the E_2 series prostaglandins generated from arachidonic acid, an omega-6 fatty acid that is produced from linoleic acid in animals (152, 153). EPA inhibits the formation of the E_2 series prostaglandins, inhibiting the formation of arachidonic acid in both young and old individuals (154, 155). In rats fed a diet high in arachidonic acid, E_2 series prostaglandins were elevated in the hippocampus, which was attenuated by feeding the rats EPA (156). Because the E_2 series prostaglandins inhibit serotonin release and EPA inhibits the generation of these prostaglandins, it seems likely that EPA in the brain would be important for normal serotonin release. Indeed, human plasma omega-3 levels have been positively correlated with the serotonin metabolite 5-HIAA in cerebral spinal fluid (157). Dietary surveys in the United States indicate that the average adult intakes of linoleic acid (omega-6 fatty acid), α-linolenic acid (omega-3 fatty acid), EPA, and DHA are ~12–20, 1.4–2.0, 0.03–0.06, and 0.05–0.10 g/d, respectively (158). These data suggest that most adults are not getting enough EPA and DHA from their diet.

EPA inhibits inflammation and depression

The E_2 series prostaglandins are hormone-like signaling molecules that play an important role in promoting inflammation, particularly by inducing the production of proinflammatory cytokines such as interleukins IL-6 and IL-1β and TNF (159). Inflammatory cytokines generated in the periphery are able to cross the blood-brain barrier and cause neuroinflammation. It has been shown that injecting endotoxin in people, which causes an immune response and the production of proinflammatory cytokines, results in depression and inhibition of verbal and nonverbal memory (160). Similarly, intravenous injection of the IFN-γ inflammatory cytokine causes depressive symptoms in people; however, the depression is ameliorated with supplementation with a high dose of EPA (161). Furthermore, individuals with gene polymorphisms in serotonin-related genes have been shown to have an even higher risk of inflammation-induced depression resulting from intravenous injection of IFN-γ (162). Although the link between depression and inflammation has been made, no mechanism has been identified. We think it is likely that the depression that occurs as a consequence of inflammation results from the inhibition of serotonin release, because serotonin also plays an important role in mood. Because serotonin regulates a wide range of cognitive functions and social behaviors in addition to mood, inhibiting the inflammatory E_2 series prostaglandins with EPA has very important serotonin-related therapeutic implications.

DHA regulates serotonin receptor function

We propose another mechanism, that the omega-3 fatty acids modulate the serotonin system is through DHA-mediated regulation of serotonin receptor function, which depends on cell membrane fluidity. DHA is the most abundant fatty acid in the brain, making up 30% of the fatty acid content (163–167). Cell membrane fluidity depends on the amount of cholesterol, which decreases membrane fluidity, and the omega-3 fatty acids in the membrane phospholipids, which increases membrane fluidity. DHA composition in the lipid membrane is necessary for adequate membrane fluidity (167–170). Cholesterol is tightly regulated in the brain, whereas fatty acid composition is influenced by dietary factors. The serotonin receptor is a G protein-coupled receptor that transverses the cell membrane 7 times and is highly influenced by the lipid membrane composition (170–172). As the membrane becomes less fluid, the binding of serotonin to its receptor decreases significantly because serotonin receptors have lower accessibility (173, 174). This effect is not limited to the serotonin receptors but also affects the dopamine receptors and other neurotransmitter receptors (175). DHA's role in membrane fluidity has also been shown to be important for synaptosomal membranes, which regulate neurotransmission (176, 177). Low omega-3 fatty acids have been associated with decreased serotonergic neurotransmission,

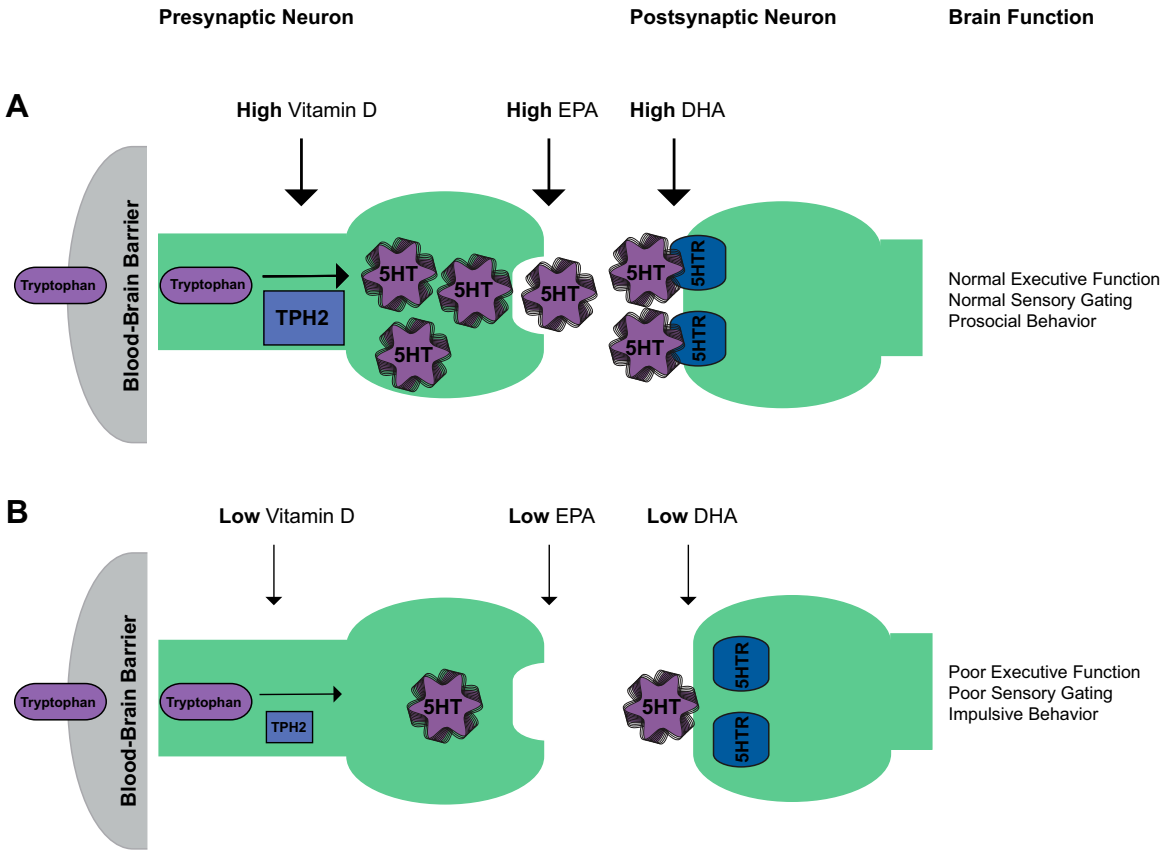

Figure 2. Micronutrient regulation of the serotonin pathway. *A*) Tryptophan is transported across the blood-brain barrier, and vitamin D sufficiency allows normal tryptophan metabolism by increasing expression of tryptophan hydroxylase 2 (TPH2) to produce serotonin (5HT). Sufficient levels of eicosapentaenoic acid (EPA) allow 5HT to be released by the presynaptic neuron. Sufficient levels of docosahexaenoic acid (DHA) allow for the binding of 5HT to the serotonin receptor (5HTR) in the postsynaptic neuron. This allows for normal serotonin neurotransmission and executive function, sensory gating, and prosocial behavior. *B*) When vitamin D status is insufficient, TPH2 is not expressed well and little serotonin is produced. Insufficient EPA status results in inhibition of 5HT release from the presynaptic neuron. Insufficient DHA status changes the serotonin receptor accessibility resulting in less 5HT binding to the serotonin receptor on the postsynaptic neuron. This leads to abnormal serotonin neurotransmission and poor executive function, poor sensory gating, and impulsive behavior.

and DHA deficiency decreases the concentration of serotonin in the frontal cortex (178, 179). Because DHA is important for cell membrane fluidity and the serotonin receptor function depends cell membrane fluidity, this suggests that DHA may be important for serotonin receptor function.

Omega-3 fatty acids regulate neurodevelopment through serotonin

Omega-3 fatty acids play a very important role during brain development, partly through their regulation of the serotonin system. Reduced intake of EPA and DHA during neurodevelopment results in decreased serotonin synthesis, storage, release, and receptor function (164). Omega-3 fatty acid deficiency also affects the structure and wiring of the developing brain as it is associated with a decrease in neurogenesis, dendritic arborization, synaptogenesis, selective pruning, and myelination (164, 165). Perinatal omega-3 deficiency in rats resulted in a 65% reduction in serotonin levels in the prefrontal cortex and correlated with a 29% reduction in mRNA expression of *tph2* (180). In contrast, supplemental fish oil during gestation and early development increased serotonin levels in the prefrontal cortex of rats and ameliorated stress-induced reductions in serotonin levels (181, 182). Supplementation with omega-3 fatty acids may be very important during pregnancy because the fetus must derive all of its omega-3 fatty acids from the mother by placental transfer (183). Therefore, there is a substantial demand on pregnant and nursing women to provide DHA to their fetuses. The third trimester of gestation is when most of the DHA in the human brain accumulates because this is the time when the brain experiences a growth spurt (184). However, pregnant women consume even less omega-3 fatty acids than the general population, which is already deficient in omega-3, because of the concern over mercury in seafood, the best food source of omega-3 (184). These data suggest that dietary intake of the marine omega-3 fatty acids during pregnancy and early development can modulate the serotonin system.

PROTECTIVE ROLE OF ESTROGEN IN NEUROPSYCHIATRIC ILLNESS

ASD, ADHD, schizophrenia, and impulsive behavior disorders are more prevalent in males than females, whereas bipolar disorder is equally common (22, 185–188). We proposed that this sex difference in ASD is because of the fact that estrogen, a steroid hormone, can replace vitamin D hormone in activating the *TPH2* gene, thus raising serotonin levels (22). Because estrogen significantly increases the expression level of *TPH2* in the brain, serotonin levels would also be raised (189–193). Therefore, we posit that estrogen would also be protective against other neuropsychiatric illnesses. Consistent with this proposal, rats, mice, and humans all have higher tryptophan hydroxylase activity in females compared with males (194–199).

Estrogen increases serotonin synthesis, thus resulting in a protective effect on learning, memory, impulse control, and sensory gating impairments that are experimentally induced during acute tryptophan depletion (200–204). For example, the negative effects of tryptophan depletion on verbal memory are ameliorated in women who are treated with estrogen (201). Estrogen is likely to have positive effects on social behavior, as shown by the fact that women are less aggressive and commit fewer violent crimes and are less likely to commit suicide (78). Acute tryptophan depletion in women in the luteal phase of their menstrual cycle, when estrogen levels are low, causes them to be more aggressive than at other periods of the menstrual cycle when estrogen is more abundant (205). Along the same lines, in postmenopausal women, when estrogen is low, acute tryptophan depletion has significant effects on cognitive function and emotional regulation, reducing working memory and causing hyperactivation of the amygdala, which can be reversed by estrogen administration (200). These data are consistent with the hypothesis that estrogen activation of *TPH2*, and consequently increase in brain serotonin, is a mechanism by which females are somewhat protected from many of the impairments associated with neuropsychiatric disorders including executive function, sensory gating, and social behavior dysfunction.

Although estrogen may play a general protective role against many neuropsychiatric diseases in women, decreases in estrogen levels that occur during the postpartum and postmenopausal periods may leave women vulnerable to mental illness, particularly bipolar disorder, at the time of these biochemical changes. There is a precipitous drop, between 100- and 1000-fold, in estrogen levels during the first 4 months postpartum, possibly exacerbating the effects of already low vitamin D, tryptophan, and omega-3 fatty acid levels (206–208). The postpartum period has been shown to trigger the first presentation of bipolar illness or postpartum psychosis, and during this time, there is a risk for infanticide and maternal suicide, along with other problems in cognitive dysfunction (209, 210). Misdiagnosis of bipolar disorder as postpartum depression is common (211). These data suggest that the postpartum period may present a unique situation where estrogen, vitamin D, tryptophan, and omega-3 levels are all especially low, and this may create an environment for the manifestation of bipolar disorder.

DISCUSSION

We propose that serotonergic dysfunction is a common denominator in a wide range of neuropsychiatric illnesses including ASD, ADHD, bipolar disorder, schizophrenia, impulsive behavior disorders, and depression. This proposal is based on evidence that executive function, sensory gating, and prosocial behavior are all regulated by serotonin and that serotonin levels are low and polymorphisms in serotonin-related genes are common in many of these disorders. We propose that an underlying mechanism is by vitamin D hormone regulating serotonin synthesis, thus modulating the severity of the aforementioned defects. We also provide evidence supporting mechanisms by which EPA regulates the release of serotonin by inhibiting the production of E_2 series prostaglandins and DHA controls serotonin function by increasing neuronal cell membrane fluidity. Our proposed mechanism explains how vitamin D and the marine omega-3 fatty acids work in concert with each other to improve cognitive function, health, and behavior. This synergy can be explained in part by their effects on the serotonin system: vitamin D regulates serotonin synthesis, EPA influences serotonin release, and DHA improves membrane embedded serotonin receptor accessibility. It also partially explains why supplementation with vitamin D, EPA, and DHA improves some behaviors associated with ADHD, bipolar disorder, schizophrenia, and impulsive behavior by controlling serotonin production and function. Although many intervention studies with vitamin D, EPA, and DHA have shown an apparent benefit, larger clinical trials need to be done to determine efficacious doses for these various disorders.

We also review evidence demonstrating how estrogen can overcome the defects on sensory gating and executive function when serotonin is experimentally lowered. We propose that this effect may be caused by estrogen's ability to activate *TPH2*, thus explaining the lower female prevalence in psychiatric disorders. The role of the activating VDRE found in *TPH2* offers a novel explanation of why vitamin D hormone is required for normal serotonin synthesis in the brain and of how low vitamin D could affect the trajectory and development of neuropsychiatric illness. Likewise, estrogen's capacity to boost *TPH2* expression serves as an explanation of why females are more protected from mental illness.

Importantly, because vitamin D regulates the synthesis of serotonin, EPA regulates its release from neurons, and DHA regulates serotonin receptor function, adequate vitamin D and ω-3 fatty acid status would be critical to prevent defects in executive function, impulse control, sensory gating, and prosocial behavior, particularly in the context of a person with a polymorphism in a serotonin-related gene (**Fig. 2*A***). Therefore, inadequate vitamin D and omega-3 fatty acid status, in combination with genetic factors that cause dysfunction in the serotonin pathway, may exacerbate defects and trigger mental illness (Fig. 2*B*). The timing of vitamin D and/or omega-3 deficiency in combination with genetic propensity for serotonin dysfunction is also likely to be an important determinant of whether mental illness will emerge. In fact, alterations in the migration of GABAergic interneurons during brain development, which is regulated by serotonin, is a key determinant for susceptibility to psychiatric disorders such as schizophrenia and

autism (111). This may partly explain why neonatal vitamin D status is linked to the risk of schizophrenia (98, 120).

Other environmental factors, including stress hormones and inflammatory cytokines, also regulate tryptophan metabolism. Stress hormones and inflammatory cytokines activate the rate-limiting enzymes, indoleamine 2,3-dioxygenase (*IDO*) and tryptophan 2,3-dioxygenase, causing tryptophan to be metabolized to kynurenine instead of serotonin (212). This means that stress and inflammation act as a tryptophan trap, shunting it away from being transported into the brain for serotonin synthesis by TPH2 (Fig. 1). In the context of prenatal stress, this would mean less maternal serotonin available to shape the developing brain, which has been shown to cause abnormal brain development in mice (110). Furthermore, prenatal stress has also been shown to cause aberrant GABAergic interneuron migration and disrupt serotonin neurons in the developing brain, both of which are associated with increased schizophrenia risk (213, 214). Early stressful events also depress the expression of *TPH2*, which decreases serotonin production in the brain and causes anxious behavior in mice (215). The effects of stress on tryptophan metabolism also lead to a positive feedback loop that ultimately causes a reduction in brain serotonin production and release. This is because of the fact that stress hormones decrease serotonin levels and low serotonin leads to anxious behavior, which results in the production of more stress hormones, thus perpetuating a vicious cycle. In the context of individuals that have polymorphisms in serotonin-related genes, stressful events and micronutrient deficiencies may be the perfect storm to precipitate mental illness. For this reason, it is imperative to break this vicious cycle to normalize serotonin levels and function in the brain while improving behavior.

The nutritional regulators of the serotonin pathway, including vitamin D, EPA, and DHA, are one easy way to intervene and optimize serotonin synthesis and function in the brain. Tryptophan and 5-hydroxytryptophan may be other methods of increasing brain serotonin and have been shown to positively affect mood and lower anxiety (37–39, 216). However, one potential concern with supplementing with tryptophan and 5-hydroxytryptophan is that they may be immediately converted into serotonin in the gastrointestinal tract, which lowers the bioavailability for transport into the brain and is known to cause inflammation (216, 217). Exercise, which increases tryptophan transport into the brain and thus serotonin production, is another simple solution to break the vicious cycle (Fig. 1).

Exercise increases tryptophan transport across the blood-brain barrier by alleviating competition with branch-chain amino acids because muscle preferentially absorbs them (218).

Many individuals with mental illness are deficient in many micronutrients, particularly vitamin D, and ω-3 fatty acids (219). This may explain why supplementation with these essential micronutrients has been shown to be effective for treating symptoms associated with ADHD, bipolar disorder, schizophrenia, impulsive behavior, depression, and obsessive compulsive disorder (142, 220). Furthermore, vitamin D and ω-3 fatty acid supplementation would be a safer therapeutic treatment than serotonin-enhancing drugs, which often have negative side effects (221). Reasonable daily therapeutic doses of ω-3 fatty acids from fish oil appear to be ≥2 g of EPA and 1 g of DHA per day (132). We predict that supplementing with vitamin D, omega-3 fatty acids, and other key micronutrients to reach sufficiently high serum levels will boost serotonin production and function in the brain, thereby improving cognitive function and limiting impulsive behavior. However, the guidelines for vitamin D sufficiency are based on its classical role in bone homeostasis, and it is unclear whether these guidelines are sufficient to maintain nonclassical functions of vitamin D hormone in other tissues, including *TPH2* activation in the brain. Other micronutrients that affect the serotonin pathway also appear relevant, such as vitamin B_6 and iron, 2 cofactors involved in serotonin synthesis (Fig. 1). Approximately 8% of the U.S. population is deficient in vitamin B_6; some preliminary evidence suggests that vitamin B_6 may also promote moderate improvements in some behaviors (90, 222, 223). Low iron is also common in 16% of menstruating women and 29% of low-income women; iron supplementation has also been shown to help improve some behaviors (224).

Vitamin D and omega-3 supplementations are practical interventions and are of great therapeutic relevance because of the massive and widespread vitamin D and omega-3 deficiencies in the United States and in particular populations (90, 225). It is likely that relatively small dietary inadequacies in several micronutrients can precipitate a cumulative detrimental effect on the nervous system, thereby compromising cognitive function and behavior. Our findings may have important therapeutic implications for individuals with impulsive aggression toward themselves, as the case with suicide, and aggression toward others. Prisons in the United States are filled with violent offenders who have an abnormally high prevalence of impulsive aggressive behaviors (226). Lowering serotonin synthesis in a person has also been shown to play a causal role in recidivism, suggesting that improving bad behaviors may depend on serotonin levels to some degree (5). This is highly relevant for violent offenders that need to be rehabilitated and suggests that optimizing their micronutrient intake by supplementation with vitamin D, EPA, and DHA may help increase serotonin production and function and thus reduce recidivism. In general, individuals that are prone to short-term decision-making and impulsive behaviors may benefit from supplementation with vitamin D and omega-3 fatty acids. Because vitamin D and omega-3 fatty acid deficiencies are widespread, it is possible that a significant part of the population has subclinical deficiencies in serotonin production and function.

Therefore, raising the vitamin D and omega-3 fatty acid levels in the general population by supplementation could result in a concomitant rise in brain serotonin levels and function, therefore increasing normal cognitive function, the propensity for prosocial behavior, and limiting impulsive behaviors. FJ

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Note added in proof: Additionally, mice that were given calcitriol, the hormonally active metabolite of vitamin D, increased the expression of Tph2 and the serotonin metabolite (5-HIAA) in the prefrontal cortex and the hippocampus demonstrating that vitamin D hormone indeed activates Tph2 in the brain (227). It is noteworthy that these mice did not have higher serotonin levels but did have more 5HIAA, suggesting that when serotonin levels are normal, additional vitamin D increases serotonin degradation and does not raise it beyond a physiological normal concentration (227).

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