Trends in Neurosciences

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Review

Vitamin D in Synaptic Plasticity, Cognitive Function, and Neuropsychiatric Illness

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Over a billion people worldwide are affected by vitamin D deficiency. Although vitamin D deficiency is associated with impaired cognition, the mechanisms mediating this link are poorly understood. The extracellular matrix (ECM) has now emerged as an important participant of synaptic plasticity and a new hypothesis is that vitamin D may interact with aggregates of the ECM, perineuronal nets (PNNs), to regulate brain plasticity. Dysregulation of PNNs caused by vitamin D deficiency may contribute to the presentation of cognitive deficits. Understanding the molecular mechanisms underpinning the role of vitamin D in brain plasticity and cognition could help identify ways to treat cognitive symptoms in schizophrenia and other neuropsychiatric conditions.

Vitamin D and Cognition

Vitamin D deficiency affects nearly a billion people worldwide [1]. In addition to its established roles in causing rickets and osteomalacia, the convergence of *in vitro* animal and epidemiological research points to vitamin D deficiency as a candidate modifiable risk factor for a range of neuropsychiatric and neurological diseases [1]. While definitive links remain to be substantiated, vitamin D deficiency has been associated with vulnerability to various disorders including schizophrenia [2], depression [3], attention deficit disorder [4], autism spectrum disorder [5], and neurodegenerative disorders such as Alzheimer's disease and dementia [6]. A common thread to all of these disorders is impairment in cognitive functioning, which is also the most salient predictor of functional outcome. Therefore, it is essential to identify risk factors that operate at the early stages of disease, and to develop efficient primary treatment strategies to delay or prevent cognitive disturbances. This review aims to outline recent developments in our understanding of the physiological roles of vitamin D, and the impact of vitamin D deficiency on the presentation of cognitive deficits. Furthermore, we discuss evidence indicating that vitamin D deficiency may disturb properties of brain plasticity, which is likely to contribute to the presentation of cognitive disturbances. Lastly, we expound on a novel hypothesis, suggesting a link between vitamin D and PNNs, aggregate structures of the ECM.

Physiological Roles of Vitamin D in the Body and Brain

Vitamin D is a group of fat-soluble secosteroids that play important roles in the human body [7]. The two major forms of vitamin D are vitamin D_3 (cholecalciferol) and vitamin D_2 (ergocalciferol). While both cholecalciferol and ergocalciferol can be obtained through dietary sources, vitamin D_3 is typically obtained through the synthesis of cholecalciferol in the skin from 7-dehydrocholesterol by UV radiation [8]. Cholecalciferol enters the circulation and is transported by the vitamin D binding protein (VDBP) to the liver, where it is hydroxylated, resulting in the formation of calcidiol [25-hydroxyvitamin D_3 or 25(OH)D_3], the major circulating form of vitamin D [8]. 25(OH)D_3 is then transported by the VDBP to the kidneys and other tissues where it is converted by the mitochondrial enzyme 1,α-hydroxylase (CYP27B1), resulting in the hormonally active from of vitamin D, calcitriol [1,25-dihydroxyvitamin D_3 or 1,25(OH)$_2$$D_3$; Figure 1]. 1,25(OH)$_2$$D_3$ is

Highlights

Vitamin D plays various roles in normal brain physiology, including modulating synaptic plasticity.

Converging evidence suggests that vitamin D deficiency affects multiple brain processes, including cognitive functioning, in both healthy people and those afflicted with neuropsychiatric illness. The underlying mechanisms, however, are poorly understood.

Evidence suggests that vitamin D deficiency impacts synaptic plasticity through a plethora of avenues, including L-type voltage-gated calcium channels and regulation of various neurotransmitters, including NO.

An emerging concept is that vitamin D deficiency may weaken the integrity of PNNs, aggregates of the ECM, through modulation of MMPs.

PNNs have been reported to play essential roles in cognitive processes such as learning and memory. As such, dysregulation of PNNs is likely to disturb neural-circuit function and impair cognitive functioning.

Assessing the molecular mechanisms that underpin the roles of vitamin D in cognition is pertinent to informing preventive and intervention strategies for persons with cognitive disturbances, including patients with schizophrenia.

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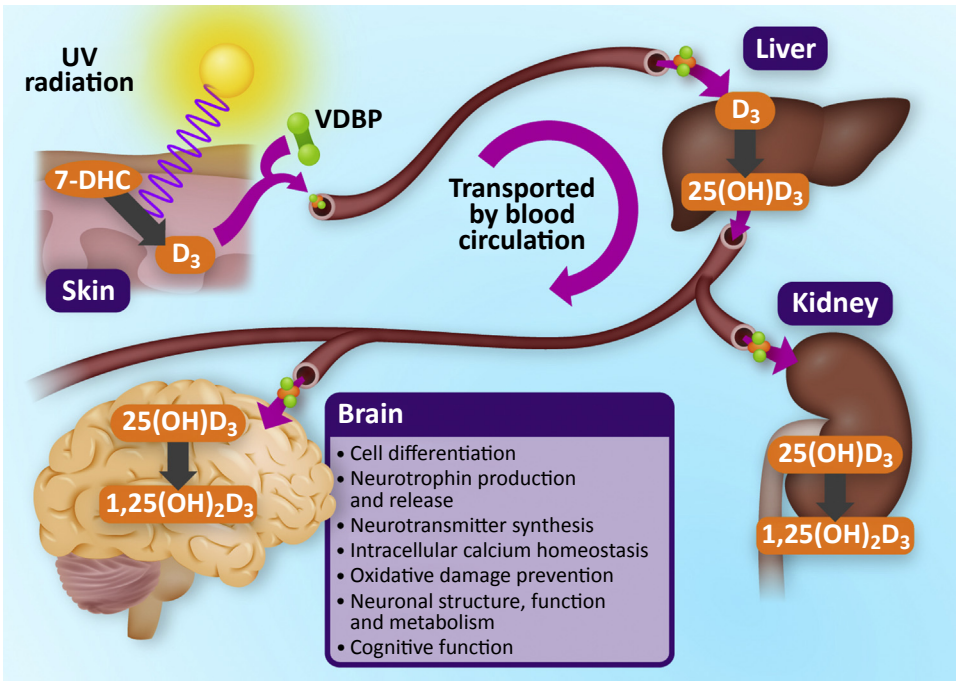

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Figure 1. Vitamin D Metabolism and Action in the Brain. Vitamin D_3 (cholecalciferol) is obtained in the skin from 7-DHC; a reaction that is facilitated by UV radiation. Cholecalciferol enters the circulation, transported in the blood by VDBP to the liver, where it is hydroxylated, resulting in the formation of 25(OH)D_3; the major circulating form of vitamin D. 25(OH)D_3 is then transported by the VDBP to the kidneys and other tissues where it is converted into the hormonally active from of vitamin D, 1,25(OH)$_2D_3$. Both 25(OH)D_3 and 1,25(OH)$_2D_3$ can cross the blood–brain barrier into the brain where 25(OH)D_3 can be converted into 1,25(OH)$_2D_3$. This ability has been found to impact on many brain processes including cell differentiation, neurotrophic production and release, neurotransmitter synthesis, intracellular calcium homeostasis, oxidative damage prevention, neuronal structure function and metabolism, and finally cognitive functioning. Abbreviations: 1,25(OH)$_2D_3$, calcitriol; 7-HDC, 7-dehydrocholesterol; 25(OH)D_3, calcidiol; VDBP, vitamin D binding protein.

responsible for most, if not all of the biological actions of vitamin D, through its binding to the vitamin D receptor (VDR) [7]. While this process is well documented in organs other than the brain, evidence suggests that the conversion of 25(OH)D_3 into 1,25(OH)$_2D_3$ may occur in the brain as well. Both 25(OH)D_3 and 1,25(OH)D_3 can cross the blood–brain barrier [9]. Furthermore, recent evidence suggests that the brain also has the necessary machinery for converting 25(OH)D_3 into 1,25(OH)$_2D_3$. It has been observed that brain endothelial cells and neurons can transform the inactive cholecalciferol into 25(OH)D_3 [10]. This can then be metabolised into 1,25(OH)$_2D_3$ by neurons or microglia before being transferred to astrocytes where it can bind to VDR and initiate gene transcription or be inactivated when in excess [10]. Furthermore, it is evident that 1,25(OH)$_2D_3$ can induce rapid nongenomic actions within the CNS, including autocrine and paracrine actions, via a membrane receptor of vitamin D known as protein disulphide isomerase family membrane (PDIA3) [10]. This effect is independent of the classical actions of the VDR and the mechanism of action has received little attention in the CNS [11].

Evidence for a role of vitamin D in brain function began with autoradiographic findings of the presence of VDR in the brains of experimental animals [12]. It is now widely accepted that VDR is found in neurons and glial cells in most regions of the brain including the cortex (temporal, frontal, parietal, and cingulate), deep grey matter (thalamus, basal ganglia, hypothalamus,

hippocampus, and amygdala), cerebellum, brainstem nuclei, substantia nigra (dopaminergic neuron-rich area), spinal cord, and ventricular system [13]. In the past decade, several studies have shown that vitamin D influences cell differentiation [14], neurotransmitter synthesis [15], neurotrophin production and release [16], intracellular calcium homeostasis [17], prevention of oxidative damage to nervous tissue [18], and expression of genes and proteins involved in neuronal structure, physiological function, and metabolism [19]. This legion of actions clearly highlights a role for vitamin D in regulating cerebral function. Recently, vitamin D has emerged as a likely candidate for modulating cognitive functioning in healthy adults.

Effect of Vitamin D Deficiency in Healthy Adults

Meta-analyses and systematic reviews have shown that vitamin D deficiency is associated with cognitive difficulties in healthy adults [20–22]. Furthermore, observational studies have shown a relationship between low vitamin D status and cognitive decline in elderly adults [23–28]. Llewellyn and colleagues [23] have suggested that vitamin D deficiency is associated with an increased risk of cognitive impairment in the elderly population. Other work also supports this finding, suggesting that those with vitamin D deficiency are more likely to attain a lower score on the Montreal Cognitive Assessment (MoCA), a widely used screening assessment for detecting cognitive impairment [27]. This effect remains significant when controlling for predictors (age, sex, and education), and after accounting for the effects of exercise.

Following up on these findings, Dean *et al*. [29] examined whether supplementation of vitamin D can lead to improvements in diverse measures of cognitive and emotional functioning in healthy young adults, compared with controls. Contrary to the hypothesis of the study, the findings indicated that vitamin D supplementation did not influence cognitive or emotional functioning in healthy young adults. This finding is supported by other studies suggesting no relationship between vitamin D and cognitive functioning in young to middle-aged adults [30–32]. However, Petterson *et al*. [33] found that high-dose vitamin D supplementation significantly improved performance on nonverbal (visual) memory, compared with low dose supplementation. This effect was particularly pronounced among those who were vitamin D insufficient at baseline. This finding aligns with other recent cross-sectional and longitudinal studies demonstrating significant positive associations between vitamin D levels and nonverbal, but not verbal, memory [34–36]. However, many questions remain and there is a need for further randomised control trials to evaluate the effects of vitamin D supplementation on cognitive outcomes in different populations.

It is possible that these discrepancies in the vitamin D literature can be attributed to cross-sectional study designs, inadequate statistical adjustment, and heterogeneity in cognitive function measures. Another possible explanation is variation across vitamin D deficiency cut-off values used in different studies. There is controversy surrounding the formal definition of vitamin D deficiency [37]. According to some authorities, including the Institute of Medicine, persons are at risk of vitamin D deficiency at serum $25(OH)D_3$ concentrations $\leq$30 nmol/l [38]. Some argue that optimal levels of serum $25(OH)D_3$ concentrations are $\geq$50 nmol/l, and persons below this level should be considered as high risk and targeted for treatment [39]. Similarly, there have been some authorities that recommend serum $25(OH)D_3$ levels of 75–80 nmol/l or higher [40]. However, these guidelines are generally based on skeletal health outcomes. It is possible that these levels may actually be insufficient for maintaining optimum functioning of other tissues and systems including the nervous system. Another possible reason for the discrepancies among the aforementioned studies relates to the idea of cognitive reserve. This concept has been proposed to explain the observation that some degree of neuropathology can yield apparent manifestations in some individuals, but not in others [41]. It is possible that

the relationship between vitamin D status and cognitive impairment is only observable in participants with a lower degree of neural compensatory mechanisms, such as elderly people. With this in mind, it is possible that deficient levels of vitamin D, occurring at key periods of neurodevelopment, may interface with genetic risk, culminating in the expression of disease state [42]. This notion is reinforced by a well-established relationship between vitamin D deficiency and some neuropsychiatric disorders, particularly schizophrenia, wherein cognitive disturbances are pervasive.

Vitamin D Deficiency and Schizophrenia

Schizophrenia is a group of neuropsychiatric disorders characterised by positive symptoms (hallucinations and delusions), negative symptoms (depression, impaired motivation, and affective flattening), and global cognitive deficits (impairments in attention, memory, disorganised thinking, and executive functioning). The development of schizophrenia is complex, driven by genetic risks interacting with multiple vulnerability factors [42]. Vitamin D deficiency has been identified as a plausible risk factor, impacting the development of schizophrenia at multiple key periods of development.

Although the onset of overt schizophrenia typically manifests during adulthood, evidence suggests that a considerable portion of its pathogenesis lies in early brain development, including the prenatal period. A plethora of animal experiments have demonstrated that transient prenatal vitamin D deficiency is associated with persisting changes in brain structure and function [43], including evidence of altered dopaminergic function [44]; one of the key clinical finding in patients with schizophrenia [45]. Furthermore, prenatal hypovitaminosis D in rats causes dysregulation of 36 brain proteins involved in several biological pathways, including oxidative phosphorylation, redox balance, cytoskeleton maintenance, calcium homeostasis, chaperoning, post-translational modifications, synaptic plasticity, and neurotransmission in adulthood [46]. A follow-up computational analysis of these results revealed that some of the identified dysregulated proteins are also disrupted in schizophrenia and/or multiple sclerosis [46].

Low vitamin D during early life has also been identified as a risk factor for the development of schizophrenia. For example, McGrath and colleagues reported an association between deficiency of vitamin D in the first year of life and an increased risk of schizophrenia in men [47]. Supporting this, another study using dried blood samples from a Danish neonatal biobank revealed that low concentrations of vitamin D in neonates was associated with a twofold increased risk of developing schizophrenia later in life [48].

Vitamin D deficiency is prevalent also in those that have recently been diagnosed with the disorder. In a case–control study, Graham and colleagues [49] measured vitamin D levels in 20 recent-onset patients with schizophrenia and 20 matched healthy participants. While there was no significant difference between vitamin D levels of patients with schizophrenia and healthy controls, lower vitamin D levels in the schizophrenia patients were associated with more severe negative symptoms and overall cognitive deficits. Similarly, in a large cross-sectional study of vitamin D levels in community-dwelling individuals with established psychosis, 49% (n = 158) were vitamin D deficient, with only 14% (n = 45) meeting criteria for sufficiency [50]. A meta-analysis performed by Valipour and colleagues [51] reviewed 19 studies published between 1988 and 2013. Of the 2804 participants, over 65% of the participants with schizophrenia were vitamin D deficient. Findings from the majority of case–control studies on the serum levels of vitamin D of patients with schizophrenia, compared with healthy controls, have also revealed a significant inverse association between vitamin D status and schizophrenia [52]. A more recent

study by Nerhus *et al*. [53] investigated vitamin D levels and cognitive function in inpatients and outpatients with psychosis and matched controls. Schizophrenia was the most common diagnosis amid those with psychosis. The participants were assessed by a cognitive test battery, a clinical protocol (including Structured Clinical Interview for DSM-IV Axis I Disorders and Positive and Negative Syndrome Scale), and a physical examination including vitamin D measurements. Vitamin D deficiency was significantly associated with decreased processing speed (i.e., Digit Symbol Coding) and decreased fluency (i.e., verbal fluency), even when age, ethnicity, IQ, patient versus control status, and substance or alcohol abuse were controlled for. These results indicate a potential association between adult vitamin D (AVD) deficiency and a decrease in cognitive functioning, particularly in processing speed and verbal fluency, in patients with schizophrenia.

About a third of patients with chronic schizophrenia do not respond to common antipsychotic medication and require clozapine to reduce psychotic burden [54]. In a recent randomised double-blind study, chronic clozapine-treated patients with schizophrenia received vitamin D (14 000 IU weekly) or placebo for 8 weeks. Although supplementation with vitamin D was not superior to placebo in reducing psychiatric symptoms or improving the metabolic parameters, it was associated with a trend towards improvement in cognitive performance [55]. However, further studies are required using larger samples and a longer duration of supplementation to confirm any procognitive effects of vitamin D.

Given these observations, it is plausible to suggest that exposure to vitamin D deficiency at key periods of development may contribute to the development of schizophrenia and moreover, the manifestation of cognitive disturbances in adulthood. Furthermore, supplementation of vitamin D may improve cognitive symptoms in these patients after diagnosis. However, despite this increasing evidence, definitive causal relationships remain to be validated, and the exact mechanism by which vitamin D impacts cognitive functioning is unknown. An emerging concept, which could address this gap, is that vitamin D impacts brain function at the level of the synapse, influencing synaptic plasticity, which in turn, may affect cognitive functioning.

Vitamin D and Synaptic Plasticity

Synaptic plasticity refers to the ability to generate new synapses, eliminate synapses, and alter the electrophysiological, molecular, and structural properties of existing synapses in response to experience. Synaptic plasticity is thought to be one of the key processes mediating learning and memory [56]. Rapidly evolving research implicates vitamin D in the process of long-term potentiation (LTP); a widely recognised mechanism of synaptic plasticity and an essential element in information storage in the brain. LTP is described as the long-lasting enhancement of synaptic efficacy as a result of tetanic stimulation in afferent neural fibres [57]. LTP is dependent on a calcium (Ca^{2+}) rise in the postsynaptic cell, through voltage-gated calcium channels (VGCC) or N-methyl-D-aspartate (NMDA) receptors.

Prenatal vitamin D deficiency has been shown to alter genes involved in synaptic plasticity [58]. Almeras and colleagues [46] found two synaptic plasticity-related genes, drebrin and neuromodulin (also known as growth-associated protein-43; GAP-43), dysregulated in prenatal vitamin-D-deficient rat brain. Drebrin is an actin-binding protein that changes the helical pitch of actin filaments [59]. There are two isoforms of drebrin: drebrin E, which predominates in the developing brain; and drebrin A, which predominates in the adult brain and is specifically expressed in neurons [59]. During development, drebrin A expression in the brain parallels with synapse formation, and dysfunction of drebrin A has been found to be altered in the dorsal lateral prefrontal cortex in post-mortem brain of patients with schizophrenia [60]. It is possible

that this dysregulation could account, in part, for the dendritic spine alterations that are seen in these patients. Similarly, GAP-43 also plays an important role in synaptic plasticity, regulating axonal growth, and neural network formation during development. Alterations in GAP-43 expression levels have been demonstrated in several brain regions of patients with schizophrenia [61,62]. Of particular note, drebrin dysfunction has been implicated in impaired cognition [63]. Taking together these lines of evidence, one might speculate that developmental dysregulation of drebrin and GAP-43 through prenatal vitamin D deficiency might not only perturb synaptic plasticity, but also contribute to the pathophysiology of schizophrenia and its associated cognitive impairments.

As complementary evidence to the link between vitamin D and synaptic plasticity, supplementation of vitamin D has been shown to upregulate multiple genes essential for synaptic plasticity, such as synaptojanin 1 and synaptotagmin 2 and calcium/calmodulin-dependent protein kinase IIδ (CaMKIIδ). Vitamin D supplementation has also been shown to upregulate receptors for several major neurotransmitters including dopamine, glutamate, and serotonin, which are necessary for normal synaptic functioning [64]. Furthermore, according to Latimer and colleagues [64], vitamin D supplementation in rats increased neuronal excitability and mitigated age-related cognitive decline.

There is strong evidence to suggest that vitamin D also plays a fundamental role in the homeostasis of calcium-mediated activities in neurons [65]. In particular, it has been shown that expression of L-type VGCCs (L-VGCCs) is associated with vitamin D signalling. Brewer *et al*. [66] found that vitamin D downregulates mRNA expression of different subunits of L-VGCC. This genomic action occurs in the nucleus, where the transcriptional activity of vitamin D is meditated by the VDR. This notion was further supported by the fact that silencing the VDR increases the expression of L-VGCCs in primary cortical and hippocampal neurons [67]. Vitamin D can also influence intracellular levels of calcium through nongenomic actions. For example, vitamin D rapidly activates protein kinases such as CaMKII, PKA, and PI3K, which then facilitate calcium influx via L-VGCCs [68], and this action occurs via the membrane receptor of vitamin D, PDIA3. L-VGCCs have been shown to exert many influences in the brain, including neurotransmitter release, changes in neuronal excitability, learning, memory, and other physiological functions [69]. Furthermore, dysfunction of L-VGCCs has been implicated in mental disorders, including schizophrenia [70]. Recent findings from a genome-wide association study (GWAS) showed that a risk allele in the L-VGCC channel gene (*CACNA1C*) was more common in schizophrenia than in controls [71]. It has also been shown that L-VGCCs regulate not only the expression of GABAergic parvalbumin-expressing interneurons but also the development of these interneurons [72]. GABAergic neurotransmission in the dorsolateral prefrontal cortex of patients with schizophrenia has been found to be reduced in a number of studies (reviewed by Lewis and colleagues [73]). It is suggested that alterations in GABAergic neurotransmission by L-VGCCs can incur modifications of neuronal connectivity, influencing long-term cognitive functions [72].

It has also been suggested that L-VGCCs regulate levels of nitric oxide (NO), a gaseous neurotransmitter implicated in synaptic plasticity [60], synaptic transmission, and neuroprotection [74,75]. NO acts presynaptically at both glutamatergic and GABAergic synapses to alter vesicle release probability [76]. Pigott and colleagues [77] have suggested that calcium influx through postsynaptic L-VGCCs provides a trigger for $LTP_{L\text{-}VGCC}$ and also stimulates neural NO synthase (nNOS); a precursor form of NO that occurs in neurons.

Evidence also suggests a strong link between vitamin D and NO. Vitamin D has been found to influence both the production of NO and expression of the enzymes responsible for its

production including inducible NO synthase and nNOS [78–80]. NO has been linked to learning and memory processes [81] and dysregulation of NO-mediated neurotransmission has been implicated in schizophrenia [82]. Yilmaz and colleagues [83] found higher levels of NO in patients with schizophrenia, compared with controls. Other studies have yielded similar results [84,85], although there is dispute in the literature regarding direction of association [86]. Taken together, it seems likely that vitamin D influences calcium related activities of L-VGCCs, via both genomic and nongenomic actions, thereby influencing the secretion of NO. These physiological changes may ultimately impact cognition and behaviour, particularly processes such as learning and memory.

The impact of AVD deficiency on behaviour has been investigated in two strains of inbred mice, C57BL/6J and BALB/c. AVD deficiency was found to result in spontaneous hyperlocomotion in both strains [87]. The C57BL/6J strain showed no other behavioural effects of AVD deficiency. However, the BALB/c AVD-deficient mice also showed altered behaviour on the elevated plus maze, a test used to measure anxiety levels, as well as altered responses to heat, shock, and sound [87]. Furthermore, male mice appeared to be more vulnerable than female mice in response to vitamin D deficiency. For example, sex-specific effects were reported for BALB/c AVD-deficient mice tested on the five-choice serial reaction time task (5-CSRTT), as a measure of attention, in which male mice made more incorrect responses than female mice [88]. Male, but not female, mice failed to learn the five-choice continuous performance task (5C-CPT) as a measure of response inhibition. By contrast, attentional performance on the 5-CSRTT was largely intact in a C57Bl/6 mouse model of developmental vitamin D (DVD) deficiency, suggesting that DVD deficiency had little to no effect on the systems governing attention in mice [89]. When tested on the 5C-CPT, sex-specific effects were reported for C57BL/6J DVD-deficient mice, in which male mice made more perseverative responses than female mice [89].

Taken together, animal model studies indicate that vitamin D impacts the synaptic integrity of the neuronal system through a plethora of avenues, and its deficiency likely results in learning and memory deficits. The question arises, what are the players involved in mediating the effects of vitamin D on synaptic plasticity?

Traditionally, synaptic plasticity has been thought of as the ability of the pre- and postsynaptic elements to alter connectivity strength in response to temporally coordinated use or disuse. However, this prevailing vision of a synapse as a bipartite entity has constrained our thinking of synaptic function and plasticity, and its role in cognition. Among other emerging concepts in synaptic plasticity, glia and ECM have been gaining attention as important participants of the synaptic machinery, lending support to the concept of the tetrapartite synapse.

Tetrapartite Synapse: Emphasis on the ECM in Synaptic plasticity

The tetrapartite synapse framework suggests that synaptic functions and plasticity result from interactions between four components: the pre and postsynaptic elements, glial processes, and the ECM (for review, see [90]). As a particular emphasis in this framework, the ECM forms an active component of neural functions and is heavily involved in synaptic regulation.

The ECM is a complex molecular network that surrounds all cells, occupying an approximately 20% volume fraction of the adult human brain [56]. There are two major types of ECM. First, a loosely organised lattice that exists ubiquitously throughout the brain and spinal cord, surrounding the synapse, filling the synaptic cleft, and interacting with cell surface receptors (Figure 2, green and light purple tracks). Second, the ECM also forms a unique, lattice-like structure that enwraps specific neurons in the brain and spinal cord, called PNNs [91] (Figure 2, green mesh surrounding

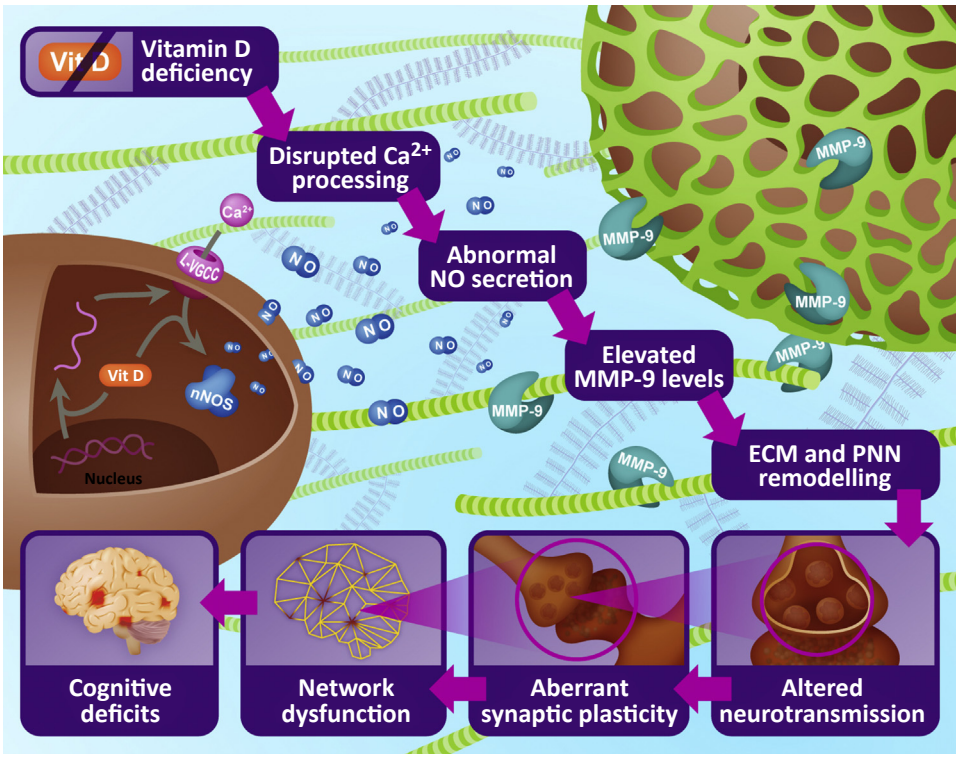

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Figure 2. Schematic Outline Depicting How Vitamin D May Impact the Integrity of PNNs in a Disease State. A neuron (brown) is depicted on the left, and a neuron with a PNN (green mesh) is depicted on the right. Collagen fibres (green) and the polysaccharides (purple) represent the loosely organised ECM, which exists ubiquitously throughout the brain and spinal cord. Vitamin D deficiency may impact the flow of calcium through L-VGCCs (depicted on the surface of the neuron) via genomic actions, moderating the transcription of L-VGCCs, and nongenomic actions, rapidly activating protein kinases such as CaMKII, PKA, and PI3K, which then facilitates calcium influx via L-VGCCs. These changes in calcium likely contribute to changes in nNOS, resulting in abnormal secretion of NO into the extracellular space. This abnormal NO secretion may increase MMP-9 levels, which are likely to impact both the ECM and aggrecan-rich PNNs, resulting in a decrease of PNN-positive cells. This decrease may perturb the excitation-inhibition balance in neuronal circuits, particularly through destabilising the activity of GABAergic interneurons that express parvalbumin. Ultimately this may produce network dysfunction resulting in the presentation of cognitive deficits. Abbreviations: CaMKII, calcium/calmodulin-dependent protein kinase II; ECM, extracellular matrix; L-VGCC, L-type voltage-gated calcium channel; MMP-9, matrix metalloproteinase-9; NO, nitric oxide; nNOS, neural NO synthase; PNN, perineuronal net; Vit D, vitamin D.

the neuron on the right). PNNs have a distinct molecular composition formed by four families of ECM molecules: hyaluronan (HA); chondroitin sulfate proteoglycans (CSPGs; i.e., aggrecan, brevican, neurocan, versican, and phosphacan); tenascins; and link proteins [92]. Although their role is still not completely understood, PNNs and their constituents, in particular HA, CSPGs, and tenascins, have been implicated in regulating synaptic activity and LTP of excitatory transmission [93–97]. For example, the pharmacological removal of HA in mice impairs LTP at CA3–CA1 synapses through occlusion of L-VGCCs, and impairs performance in hippocampal-dependent contextual fear conditioning, suggesting a functional importance for PNNs in the CNS [93]. HA has also been shown to affect both the mobility of AMPA glutamate receptors and paired-pulse modulation in hippocampal cultures [95]. Deficiency in tenascin-R results in impaired LTP, while reducing perisomatic GABAergic inhibition in the CA1 region [96]. Similarly, enzymatic removal of CSPGs also reduces LTP at excitatory synapses in CA1 [97].

Due to the proposed role of PNNs in regulating synaptic plasticity, studies have since examined the contribution of PNNs in regulating cognition. In particular, a wealth of literature has elucidated a role for PNNs in learning and memory [98–102]. While PNNs surround a variety of cells, it has been suggested that PNNs have an affinity for parvalbumin-expressing GABAergic (PV^+) interneurons. It is well established that PV^+ interneurons contribute to synchronous oscillatory activity [103,104], particularly in the gamma range (30–100 Hz), and have been shown to be involved in regulation of cognition [105–108]. Interestingly, both PNNs and PV expression are developmentally regulated and experience dependent [109]. Furthermore, the colocalisation of PV^+ interneurons and PNNs is correlated with the closure of the critical period [110]; a period of time when the maturation of the brain is strongly dependent on experience and environmental influences [111]. Recent literature highlights the possibility that dysregulation of PNNs can cause alterations in PV^+ interneuron development and activity, as well as cortical hyperexcitability [112]; a core pathophysiological mechanism thought to underlie cognitive symptoms in schizophrenia [113].

PNNs in Disease

PNNs and Schizophrenia

Recent evidence suggests that PNNs are involved in the pathophysiology of schizophrenia (for reviews, see [114,115]). Observational studies have shown in a number of human post-mortem brain studies that there is a disease-specific reduction in the density of PNNs as well as altered expression of genes that regulate PNNs and ECM in key brain structures associated with schizophrenia, including the amygdala, olfactory epithelium, entorhinal cortex, superior temporal cortex, and prefrontal cortex [116,117]. Pantazopoulos and colleagues [117] noted that the numerical density of PNNs was reduced as much as tenfold in patients with schizophrenia; however, it was unchanged in those with bipolar disorder. Furthermore, the authors revealed abnormalities affecting CSPGs; a main component of PNNs [92]. They found increases in CSPG-positive glial cells in the amygdala and entorhinal cortex in patients with schizophrenia, suggesting a possible role for ECM–glial interactions in the pathophysiology of schizophrenia. CSPGs influence neuronal migration, synaptic maturation and stabilisation, neural circuit formation, and structural plasticity; processes that are postulated to be disrupted in schizophrenia [117].

Together, these results highlight that PNN dysregulation may contribute to several aspects of the pathophysiology of schizophrenia, including possible disrupted connectivity and neuronal migration, synaptic anomalies, as well as altered GABAergic, glutamatergic, and dopaminergic neurotransmission. It is likely that these changes in PNNs occur via mediated cleavage and/or reorganisation during development.

Mechanism of PNN Dysregulation

PNN abundance is typically modulated by proteolytic processing. While animal studies often use enzymes, notably hyaluronidase or chondroitinase ABC, to experimentally degrade PNNs and examine behavioural and cognitive implications [118–120], in physiological settings, modulators of PNNs include elements such as matrix metalloproteinase (MMP) and a disintegrin and metalloproteinase with thrombospondin motifs (ADAMTSs) [121].

These two families of endogenous, extracellular metalloproteinases are zinc-dependent proteases, mostly secreted as inactive proenzymes that cleave ECM components. Although this cleavage is part of a normal turnover process of the ECM, its dysregulation may be involved in disease conditions. This is supported by several observations suggesting that MMPs are key mediators of PNN degradation. Two members of this group of ECM-regulating enzymes, MMP-

2 and MMP-24, have been shown to have direct CSPG-degrading properties in the brain [122,123] and more PNNs are expressed in juvenile MMP-9-null mice [124]. In addition, ADAMTS can mediate degradation of brevican [125] and it has been shown to be colocalised with areas of synaptic loss in a kainic acid model of acute neuronal toxicity [126]. A GWAS has identified MMP-16 as a schizophrenia risk gene [127]. Furthermore, pyramidal neurons from layer 3 of the superior temporal gyrus of patients with schizophrenia, exhibit alterations in genes that encode both MMPs and ADAMTSs, including MMP-16 [128]. In addition to MMP-16, multiple studies have supported a link between MMP-9 and schizophrenia. A functional polymorphism of the MMP-9 gene was discovered in human schizophrenia patients [129,130]. Additionally, Yamamori *et al*. [131] showed elevated MMP-9 levels in the plasma of schizophrenic patients. Peak MMP-9 expression is observed during postnatal development and is reduced during adulthood, aligning with the typical developmental timeline of schizophrenia [124]. High levels of MMP-9 contribute to proteolytic cleavage of ECM, creating an extracellular environment permissive for synaptic plasticity. As aggrecan, a component of PNNs, has been previously identified as an MMP-9 target [132], aggrecan-rich PNNs may be unstable in the presence of MMP-9, leading to abnormal development and neural excitability [124]. Well-known factors that purportedly promote schizophrenia, such as chronic stress [133] and neurotrauma [134], enhance MMP-9 levels in the brain.

PNNs and Vitamin D: Is There a Link?

Mounting evidence indicates that deficiency of vitamin D is associated with increased MMP-9 production [135,136]. For instance, Moradi and colleagues [136] investigated the association of serum levels of vitamin D and MMPs in patients with coronary artery disease (CAD). They found that there was a significant inverse correlation between MMP-9 concentrations and serum vitamin D levels in patients with CAD, such that the patients with low levels of vitamin D had high levels of circulating MMP-9. Consist with this result, Timms *et al*. [137] showed that supplementation of vitamin D can reduce circulating levels of MMP-9. Other evidence implicates a role for NO in modulating MMP-9 levels [138–140]. It has been shown that NO regulates MMP-9 activity and the activity of its endogenous inhibitor, tissue inhibitor of metalloproteinase (TIMP) 1 at both the mRNA and protein levels [139]. As mentioned earlier, vitamin D is known to regulate expression of NO [78–80]. With this in mind, along with the points discussed earlier, the following cascade for the downstream effects of vitamin D deficiency seems plausible: vitamin D deficiency may impact calcium activities in neurons, causing changes in NO secretion that may increase circulating levels of MMP-9. This is likely to have remodelling effects on the ECM, particularly on aggrecan-rich PNNs, causing synaptic anomalies and altered GABAergic, glutamatergic, and dopaminergic neurotransmission, which are likely to result in network dysfunction and cognitive deficits (Figure 2). In support of this hypothesis, a recent study in BALB/c mice found that AVD deficiency was associated with impaired hippocampal-dependent spatial memory, disrupted structural brain connectivity, and a reduced density of PNNs within the hippocampus [141]. Therefore, it seems likely that vitamin D deficiency impacts PNNs, altering hippocampal synaptic plasticity and learning and memory processes.

Concluding Remarks and Future Directions

In this review we have attempted to delineate the contribution of vitamin D to brain physiology, and the possible mechanisms linking vitamin D deficiency to cognitive deficits, including those observed in neuropsychiatric disorders, with a focus on schizophrenia. Evidence suggests that vitamin D deficiency may affect synaptic plasticity, leading to a decline in cognition. An emerging concept is that vitamin D deficiency may weaken the integrity of PNNs through modulation of MMPs, thereby distorting neural-circuit function and ultimately impairing overall cognitive functioning. This conceptual framework points to vitamin D deficiency as a modifiable

Outstanding Questions

Guidelines for vitamin D intake are generally based on skeletal health outcomes. Given that vitamin D is correlated with cognition and neuropsychiatric disease, what is the optimal level of circulating vitamin D for healthy brain function?

Is there an effective dose and duration of vitamin D supplementation for the treatment of cognitive symptoms?

When is the best time to supplement with vitamin D during the lifespan for prevention of neuropsychiatric illness?

How does serum vitamin D deficiency influence vitamin D metabolism in the brain?

Does vitamin D deficiency influence PNN degradation and/or impair PNN formation through elevated levels of MMPs in the brain? And if so, does this disruption occur in specific brain regions, or is it a general phenomenon across the brain?

If there are vulnerable brain regions in response to vitamin D deficiency, exhibited by PNN degradation, is this pattern consistent with network connectivity deficits seen in patients with schizophrenia that may relate to cognitive dysfunction (i.e., default mode network)?

If vitamin D deficiency leads to PNN degradation, does this correlate with learning and memory deficits/facilitation? And if so, can these effects be replicated by artificial enzymes (i.e., chondroitinase or hyaluronase) that degrade PNNs experimentally?

risk factor for the development of cognitive deficits, including in the healthy elderly population and in patients with schizophrenia. A goal for future studies would be to refine our mechanistic understanding of the possible links between vitamin D and cognition (see Outstanding Questions). Further investigation into the links between vitamin D deficiency and cognitive disturbances, including those seen in schizophrenia, is pertinent to inform ways to address the pressing need for new and effective preventive and intervention strategies.

Acknowledgements

This work was supported by the National Health and Medical Research Council grant APP1070081 to T.B. and a University of Queensland PhD Scholarship to P.M. The funding bodies had no role in the writing of the manuscript, and in the decision to submit the article for publication. We thank Dr Nick Valmas for preparing the illustrations. The authors have no conflicts of interest to declare.

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