



REVIEW

Schizophrenia: implications of vitamin D deficit on brain development

Ana Dias Amaral¹, Conceição Calhau^{2,3}, and Rui Coelho^{1,4}

Abstract

Background: Schizophrenia is one of the most disabling psychiatric disorders, with serious consequences on families and society. Although a genetic component in its aetiology is indisputable, environmental factors also play an important role. Vitamin D (VD) has been implicated in central nervous system development and some evidence points to its role on schizophrenia aetiology. We aim to summarize brain alterations occurring in schizophrenia and how VD is relevant to them.

Methods: Literature review up to 30th September 2014, using MeSH terms schizophrenia, vitamin D, brain, and central nervous system.

Results: We summarize alterations occurring at anatomical and histological levels. Moreover, we describe biological pathways in which VD is involved that are proven to be disrupted in schizophrenia: neurotrophic factors, neurotransmission, synaptic and cytoskeleton anomalies, calcium homeostasis, energy metabolism and redox balance. Finally, we give some emphasis to cognitive disturbances.

Conclusions: The heterogeneity of some studies does not allow to definitely affirm that VD deficit plays a role on schizophrenia aetiology. Studies on different populations and animal models should be conducted in order to achieve reproducible results. Therefore, this paper should be regarded as a guide to the pathways and anatomical structures disrupted by VD deficit in schizophrenia, and warrant further investigation. Although we cannot definitely affirm that VD deficiency is essential for schizophrenia aetiology, literature currently points to this hypothesis.

Keywords: Central nervous system, Psychotic disorders, Schizophrenia, Vitamin D.

¹Psychiatry and Mental Health Clinic, Centro Hospitalar de São João, Porto, Portugal

²Department of Biochemistry, Medical Investigation Centre, Faculty of Medicine, University of Porto, Porto, Portugal

³CINTESIS - Center for Research in Health Technologies and Information Systems, University of Porto, Porto, Portugal

⁴Department of Clinical Neurosciences and Mental Health, Faculty of Medicine, University of Porto, Porto, Portugal

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Correspondence: Ana Dias Amaral
Clínica de Psiquiatria e Saúde Mental do Centro Hospitalar de São João
Alameda Prof. Hernâni Monteiro, 4200-319 Porto, Portugal
Email address: ana.s.d.amaral@gmail.com



Introduction

Schizophrenia affects 0.5-1.0% of the global population. Its clinical presentation, in adolescence or young adulthood, is characterized by positive symptoms such as auditory hallucinations and paranoid delusions, and negative symptoms such as avolition, amotivation, or blunted affect. Cognitive disturbances, especially in working memory and attention, are also common [1].

Evidence suggests schizophrenia to arise from genetic and environmental interactions. The genetic component is due to common small effect variants and rarer moderate effect variants [2]. Actually, each small-effect single-nucleotide polymorphism (SNP) confers a very small risk amplification, but altogether, SNPs account for around 50% of total heritability on a polygenic, additive basis [3, 4]. On the other hand, copy-number variants (CNVs) consist of microdeletions or microduplications representing moderate effect variants, and are present in less than 1% of patients [4]. 22q11.2 deletion, associated with velo-cardio-facial syndrome, is one of the most well-known CNVs [4]. In recent years, rare but strong-effect variants in the exome have also been implicated [3, 4]. Although some have already been identified, the large majority remains unknown [3]. History of schizophrenia in first-degree relatives is the most important risk factor [5], but history of bipolar disease also seems to increase the risk. Common genetic risk factors, as CACNA1C (alpha 1C subunit of L-type voltage-gated calcium channel) variants, point to this hypothesis [6].

In monozygotic twin studies, concordance rate for schizophrenia is around 50% [7]. It has hence become clear that genetics could not account solely for schizophrenia etiology. Numerous environmental risk factors seem to increase susceptibility to the disease, through gene-environment interactions [4]. Some epidemiologic examples are season of birth, birthplace, prenatal infection, nutrition, obstetric complications, paternal age, cannabis abuse, and socioeconomic status [5]. These events can induce functional genomic modifications—epigenetics [5]. Thus, environmental risk factors are thought to represent a second-hit in previously susceptible individuals (genetics seen as the first-hit).

In 1999, McGrath first proposed that vitamin D (VD) underlies many other previously suggested environmental risk factors [8]. Beyond its classical role in calcium phosphorus homeostasis, VD is associated with numerous biological pathways, particularly in brain development [9]. Additionally, current evidence suggests schizophrenia arises from a neurodevelopmental defect [10], disrupting early brain formation during specific, yet unknown, critical windows of susceptibility [11].

McGrath published an update to the original article in 2010 [12]. Since then, new evidence has been published. Therefore, this article aims to summarize the existing knowledge regarding schizophrenia and VD.

Methods

We have led an exhaustive review of articles indexed to Pubmed, ISI - Web of Knowledge, Scopus and EBSCO, using MeSH terms schizophrenia, vitamin D, brain, and central nervous system. Only English articles published up to 30th September 2014 were selected. After excluding duplicate papers, 179 remained. All articles discussing VD's role in normal brain development or VD's deficiency contribution for schizophrenia were selected. Due to scarcity of epidemiologic studies, experimental studies in animal models were also included. References from review articles were analysed, resulting in the additional inclusion of 32 papers. Overall, 143 papers were considered relevant for this review.

Results

Vitamin D

VD is a steroid hormone. Actually, it is not strictly a vitamin since it is synthesized in the skin upon exposure to ultraviolet B radiation; some dietary sources also provide it [9]. Classic pathway is shown in **Figure 1** [13-15]. 7-dehydrocholesterol, an intermediate in cholesterol synthesis, accumulates in the skin, undergoing a nonenzymic reaction upon exposure to ultraviolet light, yielding previtamin. This undergoes a further reaction to form the vitamin itself, cholecalciferol, which is absorbed into the bloodstream. In the liver, cholecalciferol, either synthesized in the skin or derived from food, is hydroxylated to form the 25-hydroxy derivative, calcidiol. 25-hydroxy-vitamin D3 (25-OHD3) is the circulating form, allowing the assessment of body VD levels. VD conversion to the active form 1,25-hydroxy-vitamin D3 [1,25-(OH)2D3] occurs through 1 α -hydroxylase, for long thought to be present solely in the kidney. Recent evidence has shown that 1 α -hydroxylase is also expressed in other tissues with consequent 1,25-(OH)2D3 local synthesis and its autocrine and paracrine effects [14, 15].

The presence of both VDR and 1 α -hydroxylase in brain tissue strongly points to 1,25 (OH)2D3 synthesis in central nervous system (CNS). Therefore, it can be considered as a neuroactive steroid [16] with possible autocrine and paracrine actions [17]. VDR and 1 α -hydroxylase are present in both neuronal and glial cells, in nuclei [18] and cytoplasm [19], respectively. Immunoreactivity to VDR and 1 α -hydroxylase is found in prefrontal cortex (PFC), cingulate gyrus, caudate, putamen and substantia nigra [19], suggesting a great diversity of functions in mammalian brain [20].

Why is VD a plausible risk factor for schizophrenia?

While hypovitaminoses have been almost completely banned in Western population, VD deficiency still prevails (**Table 1**) [21]. High prevalence in healthy women is especially worrisome [22, 23].

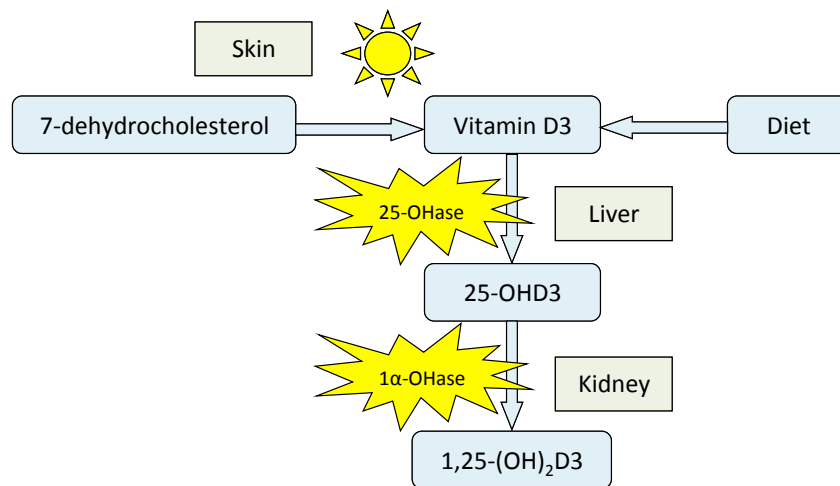


Figure 1. Classic vitamin D synthesis pathway. 7-dehydrocholesterol in skin is converted to vitamin D3 (cholecalciferol) by ultraviolet B radiation. Non-active vitamin D3 is firstly hydroxylated in liver to 25-hydroxy-vitamin D3 (calcidiol). Then, in the kidney, it suffers a second hydroxylation to its active form 1,25-hydroxy-vitamin D3 (calcitriol). 25-OHase: 25-hydroxylase; 25-OHD3: 25-hydroxy-vitamin D3; 1 α -OHase: 1 α -hydroxylase; 1,25-(OH)₂D3: 1,25-hydroxy-vitamin D3.

25-OHD3 levels appear to be inversely related to psychosis risk [25]. 25-OHD3 deficient teenagers have thrice the risk of developing psychosis, adjusted for race, body mass index (BMI), urban or rural residence and season when blood samples were collected [26]. In schizophrenic patients, 25-OHD3 is also significantly lower than in healthy controls [27-31], even at first-episode [32]. Moreover, negative and cognitive symptoms are worse when VD deficiency is present [33]. An important retrospective study conducted on a Finnish birth cohort found that vitamin D3 supplementation during the first year of life reduced schizophrenia risk by 77% in males [34]. Another study showed that low neonatal 25-OHD3 was significantly associated with schizophrenia in a Danish population. Surprisingly, very high levels are also positively associated with the disease, possibly suggesting the existence of individuals resistant to VD actions [35]. These findings were not reproduced in a different cohort in Southwest England [36].

As mentioned, numerous environmental risk factors have been associated with schizophrenia [5]. Table 2 summarizes the epidemiological risk factors that have been related with VD deficiency and the underlying rationale.

VD deficiency can apparently explain other schizophrenia risk factors, as obstetric complications, namely pre-eclampsia, which has been associated with maternal low

serum 1,25-(OH)₂D3 [45]. Reduced fertility, a schizophrenia feature, also seems to be related to low 1,25-(OH)₂D3 levels: VD is important to spermatogenesis and embryonic implantation in the placenta [46].

Finally, VD is not only an environmental risk factor but also a genetic/epigenetic one, considering VDR regulates numerous genes expression [13, 47, 48]. Unfortunately, any VDR SNP has been linked to schizophrenia yet [49].

Schizophrenia brain and VD

We have come across different neurobiological measures in our results, suggesting VD plays numerous roles in the brain.

We will start with “visible” changes—anatomical and histological. Then, we will continue with biological pathways in which VD intervenes and are proven to be disrupted in schizophrenia: neurotrophic factors, neurotransmission, synaptic and cytoskeleton anomalies, calcium homeostasis, energy metabolism and redox balance. Finally, we will analyze cognitive disturbances.

Brain gross anatomy

The most dramatic changes in cortices of rats born from VD depleted dams were larger (30%) and longer hemispheres, suggesting a distortion in early brain development [50]. Concomitantly, lateral ventricle volume was doubled compared to controls, at birth [50] and weaning [51]. Furthermore, neocortex was thinner [50]. Some of these morphological changes, specifically ventriculomegaly, persist despite VD supplementation after birth [51]. However, different groups have found ventricular volume reduction [52, 53]. A bigger striatum is a plausible explanation for this apparent volume reduction [53].

Some of these findings overlap alterations found in imaging studies in schizophrenia. Larger lateral ventricles are

Table 1. Cut off points of vitamin D levels [24].

Classification	Serum 25-OH-VD3 levels (ng/dL)
Normal	>30
Insufficiency	20–29
Deficiency	10–19
Severe deficiency	<10

Table 2. Schizophrenia risk factors and rationale for association with vitamin D.

Risk factor	Rationale for association	References
Urban environment	Less outdoor activity Reduced UVB radiation exposure Increased transmission of infectious agents	8, 37, 38
Winter birth	Reduced UVB radiation exposure Reduced photoperiod Increased exposure to infectious agents	5, 8
Latitude	Reduced photoperiod Reinforces the “winter effect”	12
Migrant status (mainly in dark-skinned)	Increased skin melanin requires more time of sun exposure for VD synthesis Higher latitudes More clothing Indoor staying	5, 39-41
Prenatal infection	VD is important in immune response against microorganisms	42-44

Abbreviations: UVB (ultraviolet B), VD (vitamin D)

one of the most constant morphological changes [54] and are present at disease onset [55]. Of note, among monozygotic twins discordant for schizophrenia, the affected twin has larger ventricles [56]. Thinner cortex is more evident in supragenual anterior and posterior cingulate and medial occipital regions [57]. Anterior cingulate cortex is important in affection, motivation, attention, and response selectivity, some of the cognitive functions affected in schizophrenia. Hippocampus and amygdala size is also reduced [54].

Histological changes

To study the origin of the anatomical changes previously mentioned in prenatal VD-deficient rats, authors investigated cell proliferation in dentate gyrus, hypothalamus, basal ganglia, amigdala, and cingulate gyrus. In all but the latter, twice the expected number of mitoses was found [50], as well as a significant apoptosis decrease due to downregulation of pro-apoptotic genes [58]. However, postnatally, authors noticed an upregulation of pro-apoptotic and downregulation of pro-mitotic genes, suggesting some sort of compensatory mechanism [58]. In adults, decreased cell proliferation was noticed in dentate gyrus, a phenomenon curiously reversed by haloperidol [59, 60].

Consistently, VD induces differentiation in hippocampal neurons, reducing mitosis, increasing nerve growth factor (NGF) and allowing axons and dendrites formation [16, 61, 62].

Periventricular and subependymal gliosis is present in schizophrenia brains, suggesting inflammation during development, but this finding is somewhat inconsistent [56]. Curiously, there are studies reporting high levels of cerebral inflammatory proteins in VD deficient animals [16].

Disrupted biological pathways

Neurotrophic factors

VD promotes NGF, glial cell line-derived neurotrophic factor (GDNF) and neurotrophin 3 (NT3) synthesis, while it decreases the levels of neurotrophin 4 (NT4) [63, 64].

Accordingly, when VD is absent prenatally, NGF levels decrease by 17% and GDNF by 25% at birth [50]. Unlike GDNF, NGF low levels persist despite VD supplementation after birth [51]. NGF is known to have trophic actions on cholinergic neurons of basal forebrain, which project to hippocampus, whereas GDNF acts on dopaminergic neurons of basal ganglia. Moreover, GDNF also controls dopaminergic neurons' apoptosis in substantia nigra, postnatally [65].

Low-affinity neurotrophin receptor (p75NTR) is significantly reduced (30%) in VD depleted brains [50]. This receptor is linked to apoptosis during development. [66]. Interestingly, cerebral distribution of both VDR and p75NTR almost overlaps [50]. Moreover, VDR progressive expression coincides with mitosis decrease and apoptosis onset occurring prior to differentiation [67-69]. Taken together, this evidence suggests that VD has an important role in both neuronal and non-neuronal development.

In schizophrenia, decreased protein kinase B (PKB) levels and function have been documented, deregulating phosphatidylinositol-3-kinase-PKB pathway, which is important in neuronal growth, differentiation and migration and is stimulated by VD [70]. We hypothesize low VD levels may impair neurogenesis through this pathway, leading to decreased PKB levels in schizophrenia.

Neurotransmission

Glutamatergic transmission: The glutamatergic hypothesis of schizophrenia has arisen by the observation that N-methyl-D-aspartate (NMDA) receptor antagonists phencyclidine and ketamine can mimic schizophrenia symptoms in healthy people [71]. Reduced glutamatergic signalling is more evident on dorsolateral PFC [72].

Neuregulin 1 (NRG1) and dysbindin, genes already associated with schizophrenia, regulate glutamate receptor subunits expression and function [73]. **Figure 2** summarizes hypomorphic NRG1 role in NMDA hypofunction and its consequences [74-77]. Hypomorphic NRG1 leads to behavioural resemblance with schizophrenia, reversed

by clozapine [74]. On the other hand, enhanced NRG1 and erbB4 (one of its receptors) interactions have been reported in schizophrenia, leading to NMDA hypofunction [75]. Hypofunction of NMDA receptors located in corticolimbic GABAergic interneurons lead to disinhibition of glutamatergic pyramidal neurons [71] and may elicit neurotoxicity [76, 77]. Hypoactive glutamatergic system may also contribute to synaptic anomalies described in schizophrenia [77].

GABAergic transmission: Glutamic acid decarboxylase (GAD) 67, GABA-synthesizing enzyme, has been found to be decreased in PFC of affected subjects [78-80], especially correlating with a reduction in parvalbumin-positive neurons [81]. GAD67 reduction was also reported in adult rats on a VD-restricted diet [82]. Moreover, as reviewed by Daviss [83], decreased number of GABAergic neurons in PFC has been reported, leading to an up-regulation of GABA receptors. Consistently, increased numbers of GABA receptors have been found in PFC and anterior cingulate cortex in schizophrenia [83]. After maternal VD deprivation, persistently decreased levels of GABA-B receptor 1 and GABA-A receptor subunit alpha-4 are noticed [51, 84].

Dopaminergic transmission: Dopamine hypothesis of schizophrenia is based on two facts: a) blocking dopamine 2 (D2) receptors diminishes positive symptoms; b) dopamine enhancing drugs induce them. Classical regions implicated in this hypothesis are striatum and nucleus accumbens. However, cognitive and negative symptoms remain unaltered by dopamine antagonists, suggesting that other regions and neurotransmitters are involved. The

current accepted dopamine hypothesis states dopaminergic neurotransmission is normal/reduced in ventral striatum, increased in associative striatum and reduced in dorsolateral PFC.

Catechol-O-methyl-transferase (COMT) is strongly associated with schizophrenia, especially in cannabis consumers [85]. Low VD causes COMT down-regulation in forebrain, consequently reducing concentrations of homovallinic acid (HVA), a marker of dopamine activity. VD supplementation reverses this [86]. Importantly, reduced levels of HVA in PFC have been associated with poor working memory in schizophrenia [87].

Differentiating factors for mesencephalic dopaminergic neurons Nurr1 and p57Kip2 have reduced expression during early brain development in VD depleted rats [86, 88, 89]. These maturation factors are only expressed after cellular division stops, consequently neuronal differentiation can begin. VD deficiency induces both cellular proliferative excess and a delay in dopaminergic ontogeny in mesencephalon during critical windows of brain development thus disrupting this pathway [88].

VDR expression in mesencephalon increases progressively from early cerebral development until weaning, in rats [18]. This concurrent VDR expression within developing dopaminergic neurons has raised considerable interest and favours a VD role in dopaminergic ontogeny [85].

Curiously, in a rat model of diabetes, overexpression of cerebellum dopaminergic receptors was normalized after VD supplementation [90]. In this perspective, it would be interesting to explore VD supplementation in schizophrenia models and its putative effects on CNS, namely, neurotransmission.

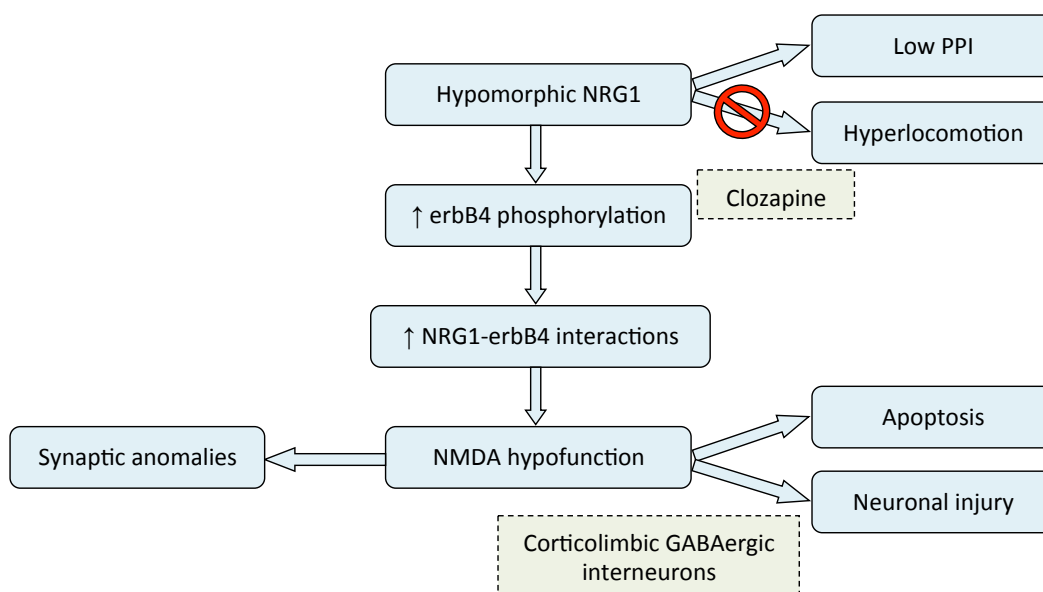


Figure 2. Hypomorphic NRG 1 leads to behavioural resemblance with schizophrenia. Unlike low PPI, hyperlocomotion is reversed by clozapine administration. By increasing erbB4 phosphorylation (one of NRG1 receptors), hypomorphic NRG1 enhances NRG1-erbB4 interactions, leading to NMDA hypofunction. Hypofunction of NMDA receptors located on corticolimbic GABAergic interneurons may elicit apoptosis and neuronal injury, as well as synaptic anomalies. NRG1: neuroregulin 1; NMDA: N-methyl D-aspartate; PPI: prepulse inhibition.

Dopamine and glutamate interactions: Reduced NMDA transmission in PFC seems to decrease mesocorticolimbic dopamine transmission thus worsening cognitive function. If sustained, it may elicit positive symptoms. Therefore, classical dopaminergic dysfunction in schizophrenia has been hypothesized to be caused by upstream abnormal glutamatergic transmission. Reduced NMDA transmission may cause both cortical dopamine deficit and associative striatum dopamine excess. Conversely, these dopamine abnormalities worsen glutamatergic function and synaptic connectivity. Glutamate and dopamine afferents from the cortex concur in striatum on GABAergic spiny neurons. Importantly, D1 receptor activation facilitates glutamatergic transmission while D2 reduces it. Thus, D1 modulation may arise as a new pharmacological target [91].

Although we have not found any reported association between glutamate and VD, we could not overlook glutamate role in schizophrenia. As reported, VD is apparently involved in dopaminergic transmission. Thus, as dopamine and glutamate are deeply interconnected, we hypothesize that some role for VD in glutamatergic transmission is yet to be found.

Synaptic anomalies

Low VD levels apparently alter the transcription of synapse proteins aquaporin-4, apolipoprotein-B, and myristoylated alanine-rich C kinase substrate [63, 84]. In one study, genes involved in presynaptic regulation had decreased expression in all the analysed schizophrenia PFC. Synapsin-2 (SYN2) and N-ethylmaleimide sensitive factor (NSF) are the most consistently down-regulated proteins (up to 74-79%) [79]. Importantly, SYN2 [84, 92] and NSF [84] were shown to be deregulated in VD deficient rats. Synaptotagmin-1, complexin-2, and synapse-associated protein 97 (SAP 97) are reduced both in schizophrenia and VD depletion [84]. In striatum, synapses show significant alterations in their organization and antipsychotic drugs seem to normalize them [93].

As previously mentioned, VD apparently controls the expression of NGF, neurotrophin and p75NTR, also important factors in synapse regulation [63].

Synaptic malfunctioning may have important consequences regarding cerebral circuits' organization and refinement. Furthermore, presynaptic genes knockout rats have long-term potentiation (LTP) deficits [94], suggesting memory formation impairment.

Cytoskeleton structure

VD deficiency reduces transcription of cytoskeletal proteins as RhoA, microtubule associated protein-2 (MAP2), GFAP [84, 92], growth associated protein-43 (GAP 43) [63], and neurofilament-light chain (NF-L) [51, 63]. MAP2 decreased transcription is persistent even after VD supplementation [51]. In nucleus accumbens, MAP-associated proteins dynamin-1 and dynamin-1-related proteins are also down regulated in VD deficiency. The same happens

for mitogen-activated protein kinase (MAPK) 1, a protein already implicated in schizophrenia [95]. These proteins are important mediators of endocytosis and crucial for D2 receptor insertion in dopaminergic neuron nonsynaptic membrane. Low GFAP levels have been found in PFC of individuals with schizophrenia [78]. MAP2 and kinesin light chain 1 (Klc1), a motor protein that moves along microtubules, have also been implicated in both conditions [84].

Cerebral calcium homeostasis

Evidence suggests schizophrenia associated VD deficiency is not severe enough to cause low serum calcium [30, 96].

VD apparently prevents neuronal free calcium uptake and consequently cellular hyperpolarization and its toxic actions [97], namely in fetal hippocampal neurons. This probably relates to the fact that VD decreases the number of L-type voltage-gated calcium channels (Cav1.2) [98], reducing calcium influx. In recent years, SNPs in the alpha 1C subunit of Cav1.2 (CACNA1C) gene have been consistently associated with increased schizophrenia risk by genome wide association studies [99]. CACNA1C is especially present in hippocampus and thalamus [6]. Hence, its polymorphisms may interfere with learning and memory processes [100]. Actually, calcium influx through Cav1.2 triggers a cascade of events that underlies hippocampus dependent memory [99]. Besides, CACNA1C plays a significant role in synaptic plasticity, neuronal survival, and dendritic development, functions already implicated in schizophrenia pathogeny. Its role in neurotransmission cannot be neglected: Cav1.2 contributes to dopamine-induced potentiation of calcium responses evoked by NMDA via D1 receptors in cortical and striatal neurons [101].

On the other hand, neurotoxic intracellular calcium is buffered by calcium-binding proteins (CBP) [97]. VD enhances the expression of two CBP, calbindin and parvalbumin [14]. Conversely, prenatal VD depletion significantly alters their expression [95]. Decreased parvalbumin-positive neurons has been highly reproduced in schizophrenia and might be explained by down-regulation of Lhx6, a transcription factor essential for migration and maturation of these neurons [102]. Reduced GABAergic neurotransmission among parvalbumin-positive interneurons and pyramidal cells is thought to contribute to working memory impairment as seen in schizophrenia [72]. Moreover, CACNA1C is known to be important to the development of parvalbumin-positive interneurons in ventral hippocampus [6].

Table 3 summarizes alterations involving parvalbumin-, calbindin-, and calretinin-positive neurons in schizophrenia.

Postnatal administration of NMDA-antagonists, mimicking schizophrenia, also reduces cortical parvalbumin expression [112-114]. Interestingly, prenatal sensitivity to NMDA antagonists decreases in a gradual manner. Simultaneously, there is an increased expression of CBP [115], mainly parvalbumin, which is expressed later in brain de-

Table 3. Calcium-binding proteins-immunoreactive neurons expression in schizophrenia.

Calcium-binding protein	Alteration	Cerebral region	References
Parvalbumin	Reduced	Prefrontal cortex	80, 81, 103, 104
		Hippocampus	103, 105
		Entorhinal cortex	103, 106
		Anterior cingulate cortex	107
Calbindin	Increased	Prefrontal cortex	83
	Reduced	Prefrontal cortex	104
		CA2	108
		Planum temporale	109
	Disarrayed	Prefrontal laminae III/IV	108
Not altered	Entorhinal cortex	106	
	Posterior cingulate cortex	110	
	Visual cortex	110	
Calretinin	Reduced	Caudate nucleus	111
	Not altered	Prefrontal cortex	80, 81, 104
		Entorhinal cortex	103
		Hippocampus	105
Anterior cingulate cortex		107	

velopment [116]. Furthermore, while calretinin expression is relatively stable during development, parvalbumin is only expressed by 3–6 months old. Calbindin distribution is also incomplete by birth [117]. These temporal disparities might explain the selective deficits of some CBP subtypes in schizophrenia—parvalbumin is expressed during a putative window of susceptibility [103].

Calcineurin, important in immune system and NMDA-mediated plasticity [73], is dependent on calcium for its activation. Its expression is disrupted in prenatal VD deficiency as well as in schizophrenia [84].

Cerebral energy metabolism

Energy production in aerobic cells implies three pathways: glycolysis in cytoplasm, Krebs cycle, and oxidative phosphorylation in mitochondrion, the essential organelle in energy production. In short, glycolysis allows glucose conversion to pyruvate. Then, pyruvate enters the Krebs cycle and origins NADH and FADH₂. These are finally broken down in the electron transport chain, yielding ATP, and H⁺ is pumped out of mitochondrion.

Hexokinase 1, the first enzyme of glycolysis pathway, and mitochondrial isocitrate dehydrogenase, a component of Krebs cycle, are down-regulated in developmental VD deficiency. Pyruvate dehydrogenase, the enzyme linking glycolysis and Krebs cycle is also decreased [95]. Electron transport chain components, NADH dehydrogenase, cytochrome B5 and somatic cytochrome C, essential to oxidative phosphorylation, are altered by prenatal VD depletion, too [84]. All in all, VD depletion causes mitochondrial malfunctioning [95].

In schizophrenia, mitochondria are scarce in many cerebral regions, a finding apparently reverted by antipsychotic drugs [84]. Moreover, regulatory genes of mitochondrial function are undoubtedly the most affected in schizophrenia PFC [118]. Numerous proteins involved in

ATP synthesis are down regulated, seriously disrupting energy production pathways [118], mainly in prefrontal and left temporal cortices [84]. Pyruvate dehydrogenase is reduced, leading to increased anaerobic respiration, and consequent increased lactate concentrations and cell acidosis. Accordingly, pH is significantly reduced in schizophrenic brains compared to controls [118]. Phosphofructokinase, hexokinase 1 and 3 and pyruvate kinase mutations have been linked to increased susceptibility to schizophrenia [119]. Overall, enzymes involved in glucose metabolism are disrupted in both schizophrenia and VD deficiency.

In short, cerebral energy appears to be compromised in schizophrenia with a shift towards anaerobic respiration, a less efficient process of ATP generation [118].

Redox balance

VD down-regulates the synthesis of inducible nitric oxide synthase (iNOS) [9]. When hypoxia is present, iNOS is activated thus liberating large quantities of nitric oxide (NO), which leads to peroxynitrite synthesis, a neurotoxic metabolite. By preventing NO synthesis, VD is a neuroprotector. In schizophrenia models, iNOS becomes significantly increased in prefrontal, perirhinal, and entorhinal cortices [120], suggesting neurotoxicity may play a role in the disease. Besides, NO is an important ion channel signalling regulator. It hinders NMDA function, directly affecting dopaminergic release [97].

In NMDA-receptor hypofunction model of schizophrenia, superoxide, a reactive oxygen species (ROS), overproduction reduces parvalbumin and GAD67 expression [121]. Superoxide dismutase (SOD) family is responsible for converting superoxide in oxygen and hydrogen peroxide, thus upregulated SOD is a surrogate for oxidative stress. SOD3, the extracellular isoform, is upregulated in schizophrenia PFC. As expected, ROS are significantly increased in this region [118]. Curiously, atypical antipsy-

chotics show antioxidant activity [122]. Moreover, VD prevents ROS cellular uptake through a not entirely understood mechanism. Conversely, hydrogen peroxide, NO and peroxynitrite preclude nuclear VD signalling by interfering with VDR.

On the other hand, physiological serum levels of VD increase glutathione expression in astrocytes [97, 123]. In schizophrenia, total glutathione levels are reduced in cerebrospinal fluid and PFC [124]. This powerful antioxidant agent can apparently regulate different neurotransmitter systems: NMDA receptor, GABA-A receptors, Cav1.2, and calcineurin. Actually, glutathione deficit leads to NMDA hypofunction [101], already discussed. It can also affect dopaminergic signalling. D1 stimulation increases Cav1.2 function, whereas D2 stimulation inhibits it. Glutathione deficit skews dopaminergic stimulation to D2 receptors [101]. In genetically-induced glutathione deficit, reduced parvalbumin expression is noticed in post-puberty, after ROS selective accumulation in ventral hippocampus [125].

Cognitive and behavioural processes

VD has been proposed to influence personality traits—increased serum levels are linked to extraversion and openness [126]. Unfortunately, this study did not consider variables influencing serum VD levels. On the other hand, schizophrenia is associated with low levels of extraversion [127].

Recently, adequate 25-OHD3 levels during second-trimester pregnancy have been linked to offspring's better mental and psychomotor development [128]. However, in adulthood, VD supplementation or restriction does not seem to lead to any cognitive alterations, in both rats [82] and humans [129]. Noteworthy, cognitive impairment is the strongest predictor of functional outcome in schizophrenia [72]. Cav1.2 has been shown to play a role in behaviours mediated by the mesolimbic pathway and amygdala [6].

Latent inhibition (LI)

LI is a learning mechanism that reflects the longer time taken for a familiar stimulus to be considered relevant comparing to a new stimulus. Schizophrenic individuals, mostly in acute episodes, show inability to ignore irrelevant stimulus—low LI. In rats, this can be replicated by maternal VD deprivation, suggesting this hormone may be linked to impairment of memory processes [130]. Apparently, this habituation deficit can be reverted by neuroleptics [131].

Prepulse inhibition (PPI)

PPI is a neurological phenomenon referring to an attenuated response to a strong stimulus if it was shortly preceded by a weaker one, usually acoustic. Its deficit in schizophrenia is thought to be linked to dopaminergic transmission overactivity in forebrain [132]. PPI impairment, a marker of reduced habituation, was not reproduced by low prenatal VD concentrations solely [133]. However, pre- and postnatal chronic VD deficiency [134], as well as VDR knockout [135] recreate this aspect.

Hyperlocomotion

Hyperlocomotion in response to novelty is a well-established feature in schizophrenia models and it has been replicated in VD depleted rats [65, 133, 136, 137]. VD deficiency also leads to hyperlocomotion in response to NMDA-antagonists [65, 96, 138, 139] and is reverted by haloperidol [65].

On the other hand, decreased exploration of surrounding environment in rats is considered homologue to negative symptoms in patients. In utero VD-deprived rats show less interest in environment exploration, mimicking apathy and difficulty in activity initiation [130]. Nevertheless, this decreased exploration was not recreated by all the other cited groups [135].

Attention and working memory

Other prominent features observed in patients, impaired attention [140] and working memory [130], are not directly affected by low prenatal VD. However, reduced dopaminergic, GABAergic and glutamatergic neurotransmission in dorsolateral PFC are linked to working memory impairment [72]. These pathways are possibly influenced by VD deficiency, as discussed throughout the text.

Discussion

Although we have divided our results in sections, it is obvious that all biological pathways interact and we believe the net effect of VD deficiency may take part in the development of schizophrenia through multiple seemingly small metabolic imbalances, as mentioned throughout this paper, and others yet to be discovered.

Some VD deficiency phenotypes have not found correspondence in schizophrenia ones, but there is much in common between them. Synapse anomalies resulting from cytoskeleton structure anomalies and neurotransmission impairment, namely glutamatergic, GABAergic, and dopaminergic are evident. Of these, NMDA hypofunction seems to be central, disrupting dopamine and GABA transmission, ultimately resulting in apoptosis and neuronal injury. Anomalies in calcium transmission, many linked to CACNA1C, are also evident and may result in NMDA hypofunction and neurotoxicity. Neuronal injury and less efficient energy production arise from anomalies in redox balance and aerobic respiration. Finally, we have noticed that anomalies in GABA, calcium, and dopamine transmission, as well as upstream glutamate abnormalities, result in working memory impairment, one of the most consistently described functional anomalies in schizophrenia. **Figure 3** aims to provide a global view of the major pathways mentioned in this paper, in a simplified manner. The global picture favours the neurodevelopmental origin of schizophrenia arising from multiple pathways' disruption, many of them also disrupted in VD deficiency models.

Current knowledge connecting schizophrenia and VD is vast but more research is needed if one aims to definitely

[141], hence a recommendation for its supplementation should be carefully addressed.

We hypothesize future anti-psychotics will target specific pathways and molecules, once they are fully characterized. Some of these will perhaps address VD-mediated pathways and phenotypes (Table 4) [37, 142].

Conclusion

Brain changes are present prior to disease onset, apparently mute, probably due to genetic polymorphisms over which VD may play an important role. Evidence suggests disease only manifests when brain and neuronal circuitries are mature, that is, in late adolescence, after a second-hit occurs (e.g., cannabis consumption). This represents a massive challenge in disease prevention and treatment.

Although we cannot definitely affirm VD deficiency is necessary for schizophrenia etiology, literature currently points to this hypothesis. In this paper, we summarized the existing knowledge and established connections among the different pieces, in hope those lacking will surface over the next years.

Abbreviations

1,25-(OH)₂D₃: 1,25-hydroxy-vitamin D₃; 25-OHD₃: 25-hydroxy-vitamin D₃; BMI: body mass index; CBP: calcium-binding proteins; CNS: central nervous system; COMT: catechol-O-methyl-transferase; D₂: dopamine 2; GABA: gamma-aminobutyric acid; GAD67: glutamic acid decarboxylase 67; GAP-43: growth associated protein-43; GDNF: glial cell line-derived neurotrophic factor; GFAP: glial fibrillary acidic protein; HVA: homovallinic acid; iNOS: inducible nitric oxide synthase; Klc1: kinesin light chain 1; LI: latent inhibition; LTP: long-term potentiation; MAP2: microtubule associated protein-2; MAPK-1: mitogen-activated protein kinase 1; NF-L: neurofilament-light chain; NGF: nerve growth factor; NMDA: N-methyl-D-aspartate; NO: nitric oxide; NRG1: neuroregulin 1; NSF: N-ethylmaleimide sensitive factor; NT3: neurotrophin-3; NT4: neurotrophin-4; p75^{NTR}: low-affinity neurotrophin receptor; PFC: prefrontal cortex; PKB: protein kinase B; PPI: prepulse inhibition; ROS: reactive oxygen species; SAP97: synapse-associated protein 97; SOD: superoxide dismutase; SYN2: synapsin-2; VD: vitamin D; VDR: vitamin D receptor.

Competing interests

The authors declare no conflict on interest.

Table 4. Main effects of developmental vitamin D deficiency.

Neurobiological measure	Effect	References
Brain morphology	Larger and longer hemispheres	50
	↑ Lateral ventricle volume	50, 51
	↓ Cortical thickness	50
Histological changes	↑ Number of mitosis	50
	↓ Apoptotic activity	58
Neurotrophic factors	↓ Levels of NGF and GDNF	50
	↓ Levels of p75 ^{NTR}	50
Neurotransmission	↓ GAD67	82
	↓ GABA-A receptor, subunit alpha-4	51
	↓ GABA-B receptor 1	84
	↓ Differentiation factors Nurr 1 and p57Kip2	86, 88, 89
	↓ COMT expression	86
Synaptic plasticity	↓ Synaptic proteins expression	63, 84
	SYN2 and NSF dysregulation	84, 92
Cytoskeleton structure	↓ RhoA, MAP2, GFAP, GAP-43, NF-L and Klc-1	51, 63, 84, 92
Calcium homeostasis	↓ Calcium-binding proteins expression	95
	↓ Calcineurin expression	84
Energy metabolism	Mitochondria malfunctioning	95
	↓ Levels hexokinase 1 and isocitrate dehydrogenase	95
	↓ Levels cytochrome B5 and somatic cytochrome C	84
Redox balance	Superoxide dismutase 2 disruption	84
	↓ Latent inhibition	130
Cognition and behaviour	↓ Prepulse inhibition	134
	Hyperlocomotion in response to novelty	65, 133, 136, 137
	Hyperlocomotion in response to NMDA-antagonists	65, 96, 138, 139
	↓ Learning on hippocampal-associated tasks	52
	↑ Impulsivity	143

Abbreviations: NGF (nerve growth factor), GDNF (glial cell line-derived neurotrophic factor), p75^{NTR} (low-affinity neurotrophin receptor), GAD67 (glutamate decarboxylase), GABA (gamma-aminobutyric acid), COMT (catechol-O-methyltransferase), SYN2 (synapsin), NSF (N-ethylmaleimide sensitive factor), MAP2 (microtubule-associated protein), GFAP (glial fibrillary acidic protein), GAP-43 (growth associated protein), NF-L (neurofilament light-chain), Klc-1 (kinesin light-chain), NMDA (N-methyl-D-aspartate), ↑ increased in vitamin D depleted rats compared to controls, ↓ decreased in vitamin D depleted rats compared to controls.

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