# 16 Vitamin D and the Brain: A Neuropsychiatric Perspective

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**Abstract**    Based on clues from epidemiology, it has been proposed that low prenatal vitamin D may be a risk factor for schizophrenia. In order to explore this hypothesis, our group has undertaken an integrated research program linking analytic epidemiology and rodent experiments. There is consistent evidence from rodents that offspring exposed to low developmental vitamin D deficiency have altered brain structure and function as adults. This chapter provides a concise summary of the evidence linking vitamin D to brain development and function. In addition, the epidemiological evidence linking hypovitaminosis D and various neuropsychiatric disorders is outlined.

**Key Words:** Vitamin D; animal experiments; neuroscience; schizophrenia; developmental neuroscience; epidemiology

## 1. INTRODUCTION

From an historical perspective, the links between vitamin D and neuropsychiatric disorders have only received attention in recent decades. The first indirect clue that vitamin D may play a role in brain development and function was when vitamin D and its metabolites were discovered in the cerebrospinal fluid of healthy adults *(1)*. However, the work of Walter Stumpf catalysed the modern interest in the impact of vitamin D on brain function. Stumpf mapped 1,25-dihydroxyvitamin D [1,25(OH)$_2$D] binding in rodent brains using radio-labelled 1,25(OH)$_2$D and autoradiography *(2, 3)*. The presence of this receptor in the central nervous system (CNS) provided the first real clues that vitamin D may have a role in brain function. Later studies using immunohistochemistry for the vitamin D receptor (VDR), in the neonatal and adult rat central nervous system, showed evidence for the VDR in multiple brain regions (e.g. temporal, orbital and cingulate cortices, thalamus, accumbens, amygdala, olfactory system and pyramidal neurons of the hippocampus), thus adding further weight to the hypothesis that vitamin D

signalling is involved in brain function *(4–6)*. The later discovery of 1-hydroxylase in the human brain suggests that the CNS can synthesise $1,25(OH)_2D$ (the active form of vitamin D) from 25-hydroxyvitamin D [25(OH)D], which is the precursor inactive form (this is the "storage" form of vitamin D used to monitor serum levels). Thus, serum 25(OH)D levels may influence the autocrine and paracrine production of $1,25(OH)_2D$ in the CNS *(7–10)*, challenging the assumption that the brain is wholly reliant on circulating 25(OH)D crossing the blood–brain barrier *(11, 12)*.

The chapter has two aims. We will provide a concise summary of the evidence linking vitamin D to brain development and brain function. Mostly, this evidence is based on animal experiments. In particular, we will focus on an animal model developed by the authors to explore the impact of transient low prenatal vitamin D on brain development. Finally, we will summarize the epidemiological clues that link vitamin D to adult neuropsychiatric disorders such as schizophrenia and depression.

## 2. VITAMIN D AND BRAIN DEVELOPMENT

Expression of the VDR is temporally regulated in the developing rat CNS *(4)*. The earliest expression of VDR in the developing brain is in neural epithelium from day 12 of gestation. The VDR continues to be expressed in differentiating areas of the brain throughout gestation *(4)*. Specifically, the VDR emerges at days 19–21 in the pyramidal cells of the hippocampus, the same time at which the cells begin to cease division and commence differentiation in this brain region *(4)*. There is also a strong correlation between the degree of VDR staining and the degree of mitotic activity seen in the developing neuroepithelium of the developing rat CNS *(6)*. The temporal expression of VDR protein and messenger ribonucleic acid (mRNA) in the developing rat brain actually coincides with a decrease in mitotic activity and an increase in apoptosis, and this has led to the hypothesis that vitamin D could be regulating neuronal cell cycle events *(6)*.

Given nerve growth factor (NGF) is essential for the growth and survival of cholinergic basal forebrain neurons which project to the hippocampus *(13)* and $1,25(OH)_2D$ is a potent regulator of NGF *(14, 15)*, it is possible that vitamin D can effect hippocampal development by modulating NGF production *(4)*. The addition of $1,25(OH)_2D$ has been shown to increase neurite outgrowth in embryonic hippocampal explant cultures, an effect which is most likely due to the induction of NGF *(16)*. The addition of $1,25(OH)_2D$ to cultured hippocampal neurons also reduces the number of mitotic cells present and increases the amount of free NGF protein produced *(16)*. NGF is capable of binding to the neurotrophin receptor p75[NTR] *(17)*. The promoter region of this receptor contains a vitamin D response element; hence, vitamin D can regulate the expression of the p75[NTR] receptor in glioma cells *(18)*. NGF and p75[NTR] are essential for programmed cell death *(19)*. As vitamin D regulates both proteins, it is possible that vitamin D could modulate neuronal survival and differentiation during development.

Vitamin D may also indirectly influence neuronal development by altering neurotrophic factor production by non-neuronal cells. The addition of $1,25(OH)_2D$ to rat primary glial cell cultures has been shown to increase the synthesis of NGF mRNA and protein *(14)*, neurotrophin-3 (NT-3) mRNA *(20)* and down-regulate neurotrophin-4 (NT-4) mRNA *(20)*. The addition of $1,25(OH)_2D$ can also increase the synthesis of glial

cell line-derived neurotrophin factor (GDNF) mRNA in C6 glioma cells *(21)* but does not regulate GDNF production in primary glial cell cultures *(22)*. While GDNF is produced by non-neuronal cells, it is integral to the development of the dopaminergic *(23)* and noradrenergic systems *(24)*. This evidence therefore suggests that vitamin D could directly alter cellular development in the brain (both neuronal and non-neuronal).

Further evidence that vitamin D can effect brain development comes from studies on non-neuronal cell lines. $1,25(OH)_2D$ is able to induce cell death pathways in rat and human gliomas *(25)* and this effect extends to multiple glioma cell lines and primary cultures from surgical specimens *(26)*. Microglial astrocytes also respond to $1,25(OH)_2D$ in models of lipopolysaccharide (LPS)-induced brain inflammation and experimental autoimmune encephalitis (EAE) *(27, 28)*. Finally, it has been shown in vitro that activated microglia can metabolise $25(OH)D$ and produce biologically active $1,25(OH)_2D$ *(29)*. This evidence, taken in light of the evidence that the enzyme 1 α-hydroxylase is present in glial *(9)*, suggests that non-neuronal cells could synthesise vitamin D locally within the brain.

## 3. BRAIN DEVELOPMENT IN THE DEVELOPMENTAL VITAMIN D (DVD)-DEFICIENT RODENT

In order to explore the impact of transient hypovitaminosis D on brain development and subsequent adult brain structure and function, the authors have developed the developmental vitamin D (DVD) deficiency model. To obtain vitamin D depletion, female Sprague-Dawley rats are kept on a vitamin D-deficient diet. Animals are housed on a 12-h light/dark cycle (lights on at 06:00 h) using incandescent lighting to avoid ultraviolet radiation within the vitamin D action spectrum. These conditions are maintained for 6 weeks prior to mating and throughout gestation. Control animals are kept under similar conditions except they receive a vitamin D-replete diet and are housed under standard lighting conditions. After the dams have littered, all dams (and corresponding litters) are placed on vitamin D-replete diet. The vitamin D-deficient dams and DVD-deficient offspring remain normocalcemic (i.e. neither the dams nor their offspring have the rickets-like phenotype that would result from more chronic vitamin D depletion). It is important to stress that this is only a *developmental* exposure, because from birth all maternal animals and offspring receive a diet containing normal levels of vitamin D. Offspring are vitamin D replete by 2 weeks of age *(30)*, and vitamin D levels, calcium, and parathyroid hormone (PTH) levels are all normal when the animals are tested as adults (i.e. 10 weeks).

As neonates, the DVD-deficient offspring have a number of anatomical changes in the developing brain, including an increase in brain and lateral ventricle size and a decrease in thickness of the neocortex *(31)*. There are also other changes in markers of neuronal development, as DVD-deficient rats showed increased numbers of mitotic cells and decreased levels of $p^{75}$ protein *(31)*. Further studies confirmed that cellular differentiation was profoundly altered in the DVD-deficient developing brain *(32)*. The level of apoptosis in the developing brains of DVD-deficient rats follows a different trajectory compared to controls; at embryonic day 19 (E19) there was no difference; however, at E21 and birth DVD-deficient rats had fewer apoptotic cells than controls

*(32)*. This difference was normalised by post-natal day 7 (P7) *(32)*. It should be noted, however, that these rats were maintained on a vitamin D-deficient diet until being tested at P7. In line with a previous study *(31)*, DVD-deficient rats also showed increased rates of mitosis at significant pre- and post-natal time points (E19, E21, P0 and P7) *(32)*. More recently the VDR was shown to be present in neurospheres cultured from the subventricular zone (SVZ) of neonatal rats *(33)*. When neurosphere cultures are made from the brains of DVD-deficient neonates, neurosphere number was increased, suggesting greater cellular division *(33)*. This same study also revealed that the addition of $1,25(OH)_2D$ decreased neurosphere number. Thus, both the presence and the absence of vitamin D are capable of manipulating cellular proliferation in developing brain cells.

The timing of the reintroduction of vitamin D appears to be important in the persistence of these developmental changes into adulthood *(34)*. The enlarged lateral ventricles seen in the DVD-deficient neonates *(31)* only persist into adulthood if the introduction of the vitamin D-replete diet is delayed until weaning. Thus, re-addition of vitamin D to the diet from birth appears to partially ameliorate the lateral ventricle changes in DVD-deficient rats *(34)*.

The adult DVD-deficient rats also have altered brain expression of genes involved in cytoskeleton maintenance (MAP2, NF-L) and neurotransmission (GABA-Aα4) *(34)*. Gene array and proteomics analysis have been used to explore gene expression in the whole brain and protein expression in the prefrontal cortex and hippocampus of adult DVD-deficient rats *(35, 36)*. These studies found that DVD deficiency resulted in significantly altered expression of 36 proteins and 74 genes involved with cytoskeleton maintenance, calcium homeostasis, synaptic plasticity and neurotransmission, oxidative phosphorylation, redox balance, protein transport, chaperoning, cell cycle control and post-translational modifications *(35, 36)*. A recent study has examined protein expression in the nucleus accumbens in the DVD rat *(37)*. While this study found small fold-changes, it identified significant alterations in several proteins involved in calcium binding proteins (calbindin1, calbindin2 and hippocalcin). Other proteins associated with DVD deficiency related to mitochondrial function and the dynamin-like proteins.

## 4. BEHAVIOUR IN THE DVD-DEFICIENT RAT AND MOUSE

By adulthood, male DVD-deficient rats show a complex behavioural phenotype. DVD-deficient rats have disrupted latent inhibition *(38)*; however, they have normal pre-pulse inhibition *(39)* and working memory *(38)*. In the open field, DVD-deficient rats display a novelty-induced hyperlocomotion *(40)* that can be abated by injection or restraint *(39, 41)*, even though they display a normal stress response in the hypothalamic pituitary axis *(42)*. Adult, male DVD-deficient rats also exhibit a sensitivity to the *N*-methyl-D-aspartic acid receptor (NMDA-R) antagonist MK-801 *(39)*. Treatment with MK-801 induces hyperlocomotion in the open field in control rats, and DVD-deficient rats responded with an even greater enhancement in locomotor activity *(39)*. The later period of gestation appeared to be most relevant for this later effect *(30)*, because rats experiencing a DVD deficiency during late gestation also showed this effect, whereas DVD-deficient rats exposed during early gestation did not *(30)*.

A mouse model of DVD deficiency has also recently been produced in two strains of mice (129/SvJ and C57BL/6 J) *(43)*. As with the rat model, one strain exhibited spontaneous hyperlocomotion in the open field arena *(43)*. However, both strains demonstrated increased frequency of head dips in a hold board arena, indicative of increased exploratory behaviour *(43)*. This is in contrast to findings from DVD-deficient rats on the hole board test *(38)*. DVD-deficient mice were also assessed on a comprehensive screen of behavioural tests, including the elevated plus maze, forced swim test, prepulse inhibition and social interaction test *(43)*. There was no effect of maternal diet or strain on performance in any of these four tests *(43)*.

## 5. VITAMIN D AND NEUROPSYCHIATRIC DISORDERS: CLUES FROM EPIDEMIOLOGY

Based on clues from epidemiology, it has been proposed that low prenatal vitamin D may be associated with an increased risk of several adult-onset disorders. For example, McGrath *(12)* drew attention to diseases such as multiple sclerosis and schizophrenia that had both season of birth effects (e.g. those born in winter and spring have an increased risk of developing schizophrenia) and latitude effects (e.g. the prevalence of schizophrenia and multiple sclerosis is higher at higher latitudes).

Many studies have shown that those born in winter and spring have a significantly increased risk of developing schizophrenia *(44)* and that those born at higher latitudes are also at increased risk *(45)*, with both the incidence and the prevalence of schizophrenia being significantly greater in sites from higher latitudes *(46)*. Furthermore, based on data from cold climates, the incidence of schizophrenia is significantly higher in dark-skinned migrants compared to the native born *(47)*. Given that hypovitaminosis D is more common (a) during winter and spring, (b) at high latitudes and (c) in dark-skinned individuals *(48)*, low prenatal vitamin D "fits" these key environmental features. Preliminary evidence from analytical epidemiology studies also links low prenatal vitamin D with schizophrenia risk. For example, vitamin D supplements in the first year of life significantly reduced the risk of schizophrenia in males in a large Finnish Birth Cohort *(49)*. In addition, 25(OH)D serum levels in 26 mothers whose children developed schizophrenia were numerically (but not significantly) lower than that of 51 control mothers whose children did not develop the disease *(50)*. There was a trend-level association between low maternal vitamin D levels and schizophrenia in a subgroup of children of African-American mothers *(50)*, who would be at greatest risk of vitamin D deficiency because of their increased skin pigmentation.

There is some epidemiological data linking developmental vitamin D status and MS. The concordance rate of MS in monozygotic twins is only 30%, indicating a strong environmental influence on the development of the disease. Two northern hemisphere studies have described a season of birth effect for MS. A small Danish study described an excess of MS births in spring *(51)*, and a pooled analysis of patients from Canada, Britain, Denmark and Sweden described an increase in the percentage of people with MS born in May (spring) and a decrease in the percentage born in November (autumn) *(52)*. Other epidemiological links between vitamin D and multiple sclerosis are covered elsewhere in this book.

There is a growing body of evidence linking hypovitaminosis D and depression. First, the higher prevalence of seasonal affective disorder in high latitudes was noted by Stumpf *(53)*; however, results of randomized controlled trials of vitamin D supplements in this group have been mixed *(54–57)*. There is some evidence linking 25(OH)D levels to scores on mood scales *(55, 56)*, and hypotheses have been outlined linking vitamin D to neurotransmitters implicated in depression *(58)*. Observational studies suggest an association between low 25(OH)D levels and depression. Two studies designed primarily to examining 25(OH)D levels and performance on cognitive function have also reported an association between low 25(OH)D levels and depressed mood *(59, 60)*. However, neither of these studies included adjustments for physical activity; thus, any apparent association between 25(OH)D and mood may simply reflect that depressed individuals are less likely to go outside and thus access ultraviolet radiation.

These issues have been examined in a larger observation study *(61)*. Based on 1,283 community-based elderly residents (65–95 years), it was reported that 25(OH)D levels were 14% lower in 169 persons with minor depression and 14% lower in 26 persons with major depressive disorder compared with levels in 1,087 control individuals. Depression severity was significantly associated with decreased serum 25(OH)D levels and increased serum PTH levels. These associations persisted when controlled for activity levels. Adequately powered randomized controlled trials will be required to progress this interesting research field.

With respect to vitamin D and cognition, the results are also mixed. Several clinical studies have examined 25(OH)D levels and performance on neurocognitive measures using case–control samples. Based on patients with secondary hyperparathyroidism ($n = 21$) and matched controls ($n = 63$), Jorde and colleagues reported no significant association between 25(OH)D levels and various cognitive measures *(59)*. Another study, based on a mixed sample of 80 elderly individuals (60 years or older; half with mild Alzheimer's disease), reported no association between 25(OH)D levels and performance on a factor score derived from a large battery of neurocognitive tests *(60)*. Finally, a study based on a sample of 80 elderly individuals referred to a memory clinic reported a significant positive correlation between 25(OH)D levels and performance on the Mini Mental State Examination *(62)*. However, these studies lacked sufficient power to confidently detect small effect sizes, were not community-based and were not able to address the important potential confound of reverse causality (i.e. those with impaired cognitive ability may be less likely to go outside, and thus may develop hypovitaminosis D as a consequence of impaired cognition).

Some of these issues were addressed in a recently published study based on the large population-based NHANES III survey. The study examined the association between 25(OH)D levels and several different neurocognitive measures (including measures of attention and memory) in an adolescent group ($n = 1676$, age range 12–17 years), adult group ($n = 4747$, 20–60 years) and elderly group ($n = 4809$, 60–90 years). The study controlled for physical activity, as a proxy measure related to outdoor activity and possible ultraviolet light exposure. However, in the adolescent and adult groups, none of the psychometric measures were associated with 25(OH)D levels. In the elderly group there was a significant difference between 25(OH)D quintiles performance on a learning and memory task; however, paradoxically those with the highest quintile of 25(OH)D were

most impaired on the task, contrary to the hypotheses. Lower 25(OH)D levels were not associated with impaired performance on various psychometric measures. While this cross-sectional study indicates that 25(OH)D levels are not associated with neurocognitive performance, it remains to be seen if chronic exposure to low 25(OH)D levels alters brain function in the long term. Curiously, in vitro experiments have clearly shown that vitamin D has neuroprotective qualities *(63–67)*. For example, pretreatment with 1,25(OH)$_2$D reduces the impact of glucocorticoid-induced neuronal changes *(68)*. Thus, it may be feasible that low vitamin D reduces the ability of the brain to recover after various adverse events (e.g. hypoxia, infection/inflammation, high glucocorticoid levels related to stress). Chronic hypovitaminosis D may exacerbate the resultant neuropsychiatric impairment. A longitudinal, prospective study would be better suited to exploring this hypothesis. While the animal experimental data supports an association between low developmental vitamin D and altered brain development, the impact of hypovitaminosis D during adulthood on brain function remains to be clarified. Recently, a detailed narrative review of the field reached similar conclusions *(69)*. More animal experimental work should help clarify the role of vitamin D on adult brain function; however, more focussed analytic epidemiological experiments are also required.

## 6. CONCLUSIONS

The list of neuropsychiatric disorders with possible links to vitamin D continues to grow. Recently, developmental vitamin D deficiency has also been linked to autism spectrum disorders *(70)*. While the results from the DVD-deficient animal experiments indicate that brain structure and function is altered in rodents, it remains to be seen if this deficiency is associated with schizophrenia in humans. How vitamin D links to cognition and depression also warrants further scrutiny. Much work remains to be done in order to understand how developmental vitamin D can influence brain development.

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