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Developmental vitamin D deficiency and schizophrenia: the role of animal models

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Abstract

Schizophrenia is a debilitating neuropsychiatric disorder that affects 1% of the US population. Based on twin and genome-wide association studies, it is clear that both genetics and environmental factors increase the risk for developing schizophrenia. Moreover, there is evidence that conditions *in utero*, either alone or in concert with genetic factors, may alter neurodevelopment and lead to an increased risk for schizophrenia. There has been progress in identifying genetic loci and environmental exposures that increase risk, but there are still considerable gaps in our knowledge. Furthermore, very little is known about the specific neurodevelopmental mechanisms upon which genetics and the environment act to increase disposition to developing schizophrenia in adulthood. Vitamin D deficiency during the perinatal period has been hypothesized to increase risk for schizophrenia in humans. The developmental vitamin D (DVD) deficiency hypothesis of schizophrenia arises from the observation that disease risk is increased in individuals who are born in winter or spring, live further from the equator or live in urban vs. rural settings. These environments result in less exposure to sunlight, thereby reducing the initial steps in the production of vitamin D. Rodent models have been developed to characterize the behavioral and developmental effects of DVD deficiency. This review focuses on these animal models and discusses the current knowledge of the role of DVD deficiency in altering behavior and neurobiology relevant to schizophrenia.

Keywords

Behavior; development; dopamine; mice; rats; schizophrenia; vitamin D

The prevalence of mental illness is over 18% among adults in the USA (Substance Use and Mental Health Services Administration, 2014). Mental illness contributes significantly to premature death, lost productivity and healthcare costs to the affected individual and society

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as a whole. Although significant advances have been made in understanding the etiology of mental illness, there is still a great deal that is unknown about the specific factors that increase risk for these devastating diseases. Genetics has been shown to have a significant role in susceptibility for psychiatric disorders and genome-wide association and sparse sequencing studies have begun to identify risk loci that harbor polymorphisms and functional pathways for further study (Cross-Disorder Group of the Psychiatric Genomics Consortium 2013; Network & Pathway Analysis Subgroup of Psychiatric Genomics Consortium 2015; Ripke *et al.* 2013; Sullivan 2015). However, heritability estimates from twin studies (Kendler 2001) and more recent genome-wide single nucleotide polymorphism (SNP) analysis (Cross-Disorder Group of the Psychiatric Genomics Consortium *et al.* 2013) indicates that environmental factors and gene by environment interactions are also likely to contribute significantly to increased risk. As increased risk for psychiatric diseases is thought to depend, in part, on neurodevelopmental changes that occur early in life, the role of early environment including early life stressors, perinatal immune activation and dietary deficiencies have been examined as potential environmental factors. There are many excellent reviews on the role of perinatal and postnatal stress, maternal immune activation and *in utero* protein deficiency on disease status in adulthood (Babenko *et al.* 2015; Brown 2011; Knuesel *et al.* 2014; Tarantino *et al.* 2012). In this review, we will focus on the literature describing the role of vitamin D deficiency and increased risk for schizophrenia with a focus on animal models.

A slight but significant increased risk for schizophrenia has been observed in individuals born in winter or spring in human epidemiological studies (McGrath 2007; Torrey *et al.* 1997) and this effect increases with distance from the equator (Davies *et al.* 2003). Moreover, the offspring of individuals who migrate from more equatorial regions to colder climates are also at increased risk for schizophrenia (Cantor-Graae & Selten 2005), as are the offspring of city-dwellers in comparison to those who live in rural regions (March *et al.* 2008). There are many factors that vary across these groups including socioeconomic status, nutritional intake and exposure to pathogens, but one factor, exposure to sunlight and its effect on levels of the active form of vitamin D, 1,25-dihydroxyvitamin D_3 (hereafter referred to as vitamin D), has emerged as a focus of research. The first chemical reaction in the formation of vitamin D is driven by exposure of the skin to sunlight (Berridge 2015) and vitamin D levels are closely tied to sun exposure (Webb & Holick 1988) leading to the hypothesis that vitamin D levels are a mediating factor that increases risk for schizophrenia as well as a host of other health problems (McGrath 2001). Reports of vitamin D deficiency as a world pandemic (Holick 2008) have brought this topic into focus and accelerated the pace of research in this area.

The health benefits of exposure to sunlight were first appreciated in the last century when it was shown that exposure to the sun was curative for rickets (Hess & Unger 1921). Subsequent studies identified vitamin D as the antirachitic factor (Holick *et al.* 1982). Since then, our understanding of the function of vitamin D has expanded beyond its role in calcium and phosphate homeostasis, bone formation and maintenance. More recently, vitamin D has been described as a neuroactive steroid hormone involved in brain development and function (Garcion *et al.* 2002).

Vitamin D exerts its effects by binding to the vitamin D receptor (VDR), a member of the nuclear hormone receptor family, at vitamin D response elements (VDREs) within the promoter regions of vitamin D-responsive genes. Once activated, the VDR regulates gene expression and stimulates intracellular signaling pathways (Ryan *et al.* 2015). The VDR is ubiquitously expressed in a wide range of tissues including rodent and human brain (Burkert *et al.* 2003; Cui *et al.* 2007; Eyles *et al.* 2005) and there are thousands of VDRE in the genome (Carlberg 2014) supporting the numerous and pleiotropic effects that have been attributed to vitamin D.

The VDR is expressed in dopaminergic neurons in both human and rat substantia nigra, hippocampus and prefrontal cortex (Cui *et al.* 2013; Eyles *et al.* 2005) – regions implicated in schizophrenia. Expression in the substantia nigra in rats emerges early in development and increases until weaning (Cui *et al.* 2013). This finding along with the evidence for delayed dopamine (DA) cell differentiation (Kesby *et al.* 2013) and DA-mediated behavioral deficits in rodents exposed to developmental vitamin D (DVD) deficiency (Eyles *et al.* 2013) have led to the hypothesis that exposure to vitamin D deficiency could influence the development of dopaminergic neurons and have serious implications for the development of neuropsychiatric disease.

Although human epidemiological studies present compelling evidence for elevated risk for schizophrenia based on vitamin D production, the existence of numerous and often immeasurable environmental factors and the inherent ethical and logistical challenges of conducting developmental research in humans have led to the development of rodent models of DVD deficiency. These animal models are being used to elucidate the role of vitamin D during development on dopaminergic circuitry and behaviors with the ultimate goal of developing interventions that could alter the onset, severity or course of schizophrenia and other neuropsychiatric diseases.

An animal model of DVD deficiency

There are obvious hurdles that impede human studies of nutritional deficiencies during development and their effect on behavior later in life. For example, the inability to control for numerous and life-long environmental challenges that an individual encounters and that have the potential to affect the development of a psychiatric disease makes it difficult to specifically study the effects of perinatal exposure to a nutritional deficiency. Furthermore, longitudinal studies that span the perinatal period through adulthood, when most psychiatric diseases have their onset, are labor-intensive and logistically challenging. In addition to, and more relevant than these, logistical hurdles are the obvious ethical problems with manipulating nutritional intake during gestation and critical developmental periods. Moreover, the inability to access brain tissue in humans to evaluate underlying mechanistic changes presents an insurmountable challenge, although advances in neuroimaging have provided relevant insights. In order to circumvent these logistical and ethical hurdles, research has turned to the use of rodent models to study the effect of exposure to nutritional deficiencies during the perinatal period on brain development and neurobehavioral outcomes in adulthood.

Rodents are good models for these investigations for several key reasons. First, they have a relatively short gestation period and lifespan, making it more feasible to measure the effect of a perturbation during development into adulthood (around 60–80 days). Additionally, rodent models allow for control over the environment, making it possible to manipulate a single variable during a specific window of time while controlling for other variables as much as possible. Moreover, rodents have comparable neurobiological and physiological systems to humans – a feature that ultimately makes studies in rodents. Furthermore, rodent models have been used extensively to study behavior and specific assays have been developed to model certain aspects of schizophrenia (Table 1). Finally, there are advanced molecular and genomic tools available for rodents that enable assessment of underlying mechanisms (i.e. dysregulation of specific genes, changes in neurotransmitter systems and brain morphological differences). These reasons make rodent models ideal to study the effects of vitamin D deficiencies during developmental on neurobehavioral outcomes in adult offspring.

DVD deficiency: effects on behavior

Subsequent to the hypothesis regarding the role of DVD deficiency as a candidate risk factor for schizophrenia (McGrath 1999), McGrath and colleagues developed a rodent model of DVD deficiency to test its effects on brain development and behavior in adulthood. The DVD deficiency model exposes rodent dams to a diet completely deficient in vitamin D for 6 weeks prior to conception and through gestation until birth. After pups are born, the mother is switched back to a diet containing normal levels of vitamin D. The effects of DVD deficiency have been assessed primarily in adult offspring of outbred Sprague-Dawley rats, or in a few cases, inbred mouse strains. As DVD deficiency has primarily been associated with increased risk for schizophrenia, the behavioral assays used have focused on specific aspects of the positive (e.g. hallucinations and delusions), negative (e.g. anti-social and lack of motivation) and cognitive deficits that can be modeled in rodents. Specific endophenotypes of schizophrenia, traits that are enriched in individuals with the disease but are not necessarily symptoms, can also be assessed in rodent models. Table 2 summarizes behavioral studies assessing the effects of DVD deficiency.

Cognitive deficits

Cognitive deficits are among the core symptoms observed in schizophrenic patients, are strongly correlated with functional outcomes and are not well managed by current therapies (Green 1996; Green *et al.* 2004; Vingerhoets *et al.* 2013) making the need for more effective treatments imperative. The National Institute of Mental Health supported the Measurement and Treatment Research to Improve Cognition in Schizophrenia (MATRICS) initiative aimed at fostering a better understanding of the mechanisms underlying cognitive deficits in schizophrenia. The MATRICS identified seven domains: attention/vigilance, working memory, reasoning and problem solving, processing speed, visual learning and memory, verbal learning and memory and social cognition (Young *et al.* 2009b). Rodent models for most of these domains have been developed (Table 1) and appear to show good construct validity (Arguello & Gogos 2010; Kellendonk *et al.* 2009). Cognitive studies in rodents

exposed to DVD deficiency have focused primarily on attention/vigilance and working memory.

Attention/vigilance—Patients with schizophrenia have deficits in attentional processing. Attention is a multidimensional construct that can be divided into selective attention, or selecting the target stimulus, sustained attention or vigilance, focusing on the stimulus for a prolonged time, and attentional control in which attention is maintained despite distractions (Young *et al.* 2009b). In humans, attentional processes are measured with the continuous performance test. In rodents, the 5-choice serial reaction time task (5C-SRT) (Robbins 2002) and the 5-choice continuous performance task (5C-CPT) (Young *et al.* 2009a) are used to assess sustained attention. To date, no effect of DVD deficiency on attentional processing has been observed in rats (Turner *et al.* 2013) or C57BL/6J (B6J) mice (Harms *et al.* 2012b) in the 5C-SRT. In the 5C-CPT test, DVD deficiency resulted in increased premature responding thought to reflect increased impulsivity, and increased responding to non-target stimuli across all testing days, indicating a lack of response inhibition (Turner *et al.* 2013). Both of these behaviors could be prevented with acute treatment of the antipsychotic clozapine (Turner *et al.* 2013). The B6J mice exposed to DVD deficiency showed increased perseverative responses to the target stimuli in the 5C-CPT indicating a deficit in response inhibition (Harms *et al.* 2012b).

Latent inhibition (LI) is a learning phenomenon in which pre-exposure to an inconsequential stimulus diminishes future learning of new associations with that stimulus. The LI is disrupted in patients with schizophrenia (Lubow & Gewirtz 1995). In animal models, LI can be measured as the ability to ignore irrelevant stimuli in tests such as the shuttle box or fear conditioning. Deficits in LI in rats have been reported as a result of hippocampal lesions (Grecksch *et al.* 1999) and treatment with antipsychotics (Feldon & Weiner 1991). The DVD deficiency results in disrupted LI in the shuttle-box paradigm in rats (Becker *et al.* 2005) but not in B6J mice in a fear conditioning paradigm (Harms *et al.* 2012b).

Prepulse inhibition (PPI) is the attenuation of a startle response when the startle stimulus is paired with a non-startling prepulse. Prepulse inhibition is a well-validated and frequently used test of sensorimotor gating, the neurological process of filtering out irrelevant stimuli. Patients with schizophrenia show deficits in PPI that respond to treatment with atypical antipsychotics (reviewed in Braff *et al.* 2001). Deficits in PPI have also been observed in patients with Huntington's disease and obsessive compulsive disorder (Braff *et al.* 2001). In rodents, manipulating neurotransmitter systems implicated in schizophrenia using DA agonists and *N*-methyl-D-aspartate (NMDA) antagonists results in PPI deficits (Geyer *et al.* 2001). A recent paper using zebrafish ablated genomic screen homeobox 1 (*Gsx1*) expressing neurons using optogenetics and observed disrupted PPI. Similar PPI deficits were also observed in a *Gsx1* knockout mouse (Bergeron *et al.* 2015). *Gsx1* has been identified within a vulnerability locus in a genome-wide association study of neuropsychiatric disorders. These studies highlight the construct validity of PPI.

A study on rats reported a decrease in PPI in animals that were exposed to vitamin D deficiency throughout their entire life (perinatal + adulthood) but not those exposed only during the perinatal period (Burne *et al.* 2004b). Subsequent studies also found no PPI

deficits in response to DVD deficiency in rats (Burne *et al.* 2014; Kesby *et al.* 2006, 2012) or mice (Harms *et al.* 2008) exposed during the perinatal period alone. Additionally, PPI was not altered by the psychotomimetic MK-801 [NMDA receptor (NMDAR) antagonist] or the DA agonist, apomorphine, in DVD-deficient rats (Kesby *et al.* 2006, 2012). Prepulse inhibition is enhanced, however, after acute treatment with the psychomimetic cannabinoid agonist D^9-tetrahydrocannabinol (THC) (Burne *et al.* 2014).

Schizophrenic patients also show deficits in habituation upon repeated exposure to a startling stimulus. These deficits are thought to reflect alterations in central inhibitory mechanisms (Braff *et al.* 1992; Geyer & Braff 1982). The DVD deficiency does not appear to have any effect on acoustic startle response in rats (Burne *et al.* 2004b, Kesby *et al.* 2006, 2012) or mice (Harms *et al.* 2008). Similar to unexposed animals, acute treatment with MK-801 increases acoustic startle response in DVD-deficient rats (Kesby *et al.* 2012) while THC and apomorphine have no effect (Burne *et al.* 2014; Kesby *et al.* 2006).

Working memory, reasoning and problem solving—Patients with schizophrenia have impairments in working memory (Lee & Park 2005). However, modeling this form of memory in animals is complicated by subtle differences in how working memory is defined in humans vs. rodents. Behavioral tasks in rodents aimed at assessing working memory vary in the specific aspect being assessed (e.g. goal maintenance, memory capacity and interference control) (reviewed by Dudchenko *et al.* 2013). For the purposes of this review, we have grouped together a variety of behavioral tasks used to assess learning and memory in DVD-deficient rodents.

Rats exposed to DVD deficiency exhibited no baseline deficits in spatial working memory in the radial arm maze (Becker *et al.* 2005), learning acquisition or retention in a shuttle-box paradigm of active avoidance (Becker *et al.* 2005) or delay-dependent memory in the delay match to sample task (Burne *et al.* 2014). Moreover, there were no effects of DVD deficiency on decision-making processes in the rodent gambling task. The DVD-exposed animals showed significantly fewer omissions than control animals, suggesting an improvement in cognitive performance on this task (Peak *et al.* 2015). Rats exposed to DVD deficiency also showed decreased number of errors on the relearning session of the brightness discrimination task (Becker *et al.* 2005) indicating improved working memory. The DVD-deficient mice exhibited no deficits in fear conditioning (Harms *et al.* 2012b). One study, however, did find a significant impairment on working memory in DVD-deficient B6J mice in the olfactory tubing maze, a hippocampal-dependent learning task (Fernandes de Abreu *et al.* 2010).

Taken together, the results of these studies assessing cognitive function suggest that exposure to DVD deficiency has very subtle effects that differ based on both species (rat vs. mouse), underlying genetics (outbred vs. inbred) and behavioral task. Furthermore, to our knowledge, none of the positive findings on cognitive deficiencies have been replicated. Therefore, future studies are required utilizing expanded behavioral measures and diverse genetic backgrounds.

Positive symptoms

Some of the positive symptoms of schizophrenia such as hallucinations and delusions are impossible to assess in rodents. However, locomotion in a novel test environment is often used as a rodent model of the positive symptoms of psychomotor agitation and disorganized behavior. Rats with neonatal hippocampal lesions, a rodent model of schizophrenia, are hyperlocomotive in a novel environment (Black *et al.* 1998). Rats exposed to DVD deficiency also exhibit spontaneous hyperlocomotion in various behavioral assays including the open field (Burne *et al.* 2006; Eyles *et al.* 2006; Kesby *et al.* 2006), elevated plus maze (EPM) (Burne *et al.* 2004a) and holeboard test (Burne *et al.* 2004a, Kesby *et al.* 2006). However, these findings have not been consistent across all studies (Becker & Grecksch 2006; Becker *et al.* 2005; Burne *et al.* 2014) indicating that the hyperlocomotion resulting from DVD deficiency might be sensitive to testing conditions and environment (i.e. test duration, lighting levels, etc.).

Hyperlocomotion was also reported in 129/SvJ (129), but not in B6J inbred, mice in the holeboard test and open field but not in the EPM (Harms *et al.* 2008) indicating that behavioral changes may be specific to both the type of test and genetic background in mice. Interestingly, spontaneous hyperlocomotion was not found in rats exposed to a vitamin D-deficient diet after weaning and into adulthood indicating that gestation and the postpartum periods may be critical for the development of this behavior (Altemus *et al.* 1987; Burne *et al.* 2004a).

Spontaneous locomotion in the open field in rats exposed to DVD deficiency is blocked by acute exposure to restraint stress immediately prior to testing (Burne *et al.* 2006) – a finding that does not appear to be because of differences in Hypothalamic-Pituitary-Adrenal (HPA) axis reactivity (Eyles *et al.* 2006). However, exposure to stress also results in DA release in the brain (Anstrom & Woodward 2005) and DVD deficiency disrupts the development and functioning of the dopaminergic system (see *Dopamine* section below) providing a possible mechanism for the role of DVD deficiency and stress on spontaneous locomotion.

Negative symptoms

Negative symptoms reported in patients with schizophrenia include apathy, social deficits and lack of motivation. In rodents, exploratory behavior is used as an index of apathy and can be measured as a decrease in head dipping in the holeboard test. Rats exposed to a DVD deficiency show a decrease in head dipping, indicative of less exploratory activity (Becker & Grecksch 2006; Becker *et al.* 2005). This decrease in exploration is restored with subchronic treatment with haloperidol or the mGluR5 metabotropic gluta-mate receptor agonist, (R,S)-2-chloro-5-hydroxyphenylglycine CHPG; (Becker & Grecksch 2006). However, not all studies in rats have reported a difference in head-dipping behavior in the holeboard test (Burne *et al.* 2004a; Kesby *et al.* 2006) and a study of 129 and B6J mice exposed to DVD deficiency reported an increase in head dipping (Harms *et al.* 2008). However, interpretation of head-dipping behavior across studies may be confounded by the increased locomotor behavior in DVD-deficient animals that was observed in the latter three studies. Lack of habituation over multiple testing days in the holeboard test, as measured by head-dipping behavior, has also been reported in DVD-deficient rats (Becker & Grecksch

2006; Becker *et al.* 2005) and B6J, but not in 129 mice (Harms *et al.* 2008). Habituation in the holeboard test can be restored with subchronic treatment of haloperidol, CHPG and the atypical antipsychotic drug, risperidone (Becker & Grecksch 2006).

Lack of motivation to obtain a reward can be considered a measure of anhedonia, an aspect of depressive-like behavior. Rats exposed to DVD deficiency show decreased reward latency in the 5C-CPT task and an increase in the number of food rewards per session in the rodent gambling task suggesting increased motivation for reward (Peak *et al.* 2015; Turner *et al.* 2013). However, there was no alteration in reward latency in the 5C-SRT in rats exposed to DVD deficiency (Turner *et al.* 2013).

The DVD deficiency had no effect on immobility in another test of depressive-like behavior, the forced swim test in rats (Burne *et al.* 2004a) or mice (Harms *et al.* 2008). These data suggest that DVD exposure does not increase depressive-like behaviors, but may in fact increase motivation to obtain a reward. These findings also suggest that the underlying circuitry may differ between measures of depressive-like behavior (i.e. anhedonia vs. behavioral despair) and that exposure to DVD deficiency can have variable effects across different behaviors.

Asocial behavior is a core symptom of schizophrenia, affecting approximately one-third of patients. Social withdrawal and isolation emerge in the premorbid stage and persist throughout the illness (Wilson & Koenig 2014). Social behavior in rodents is assessed using the social interaction test (Nadler *et al.* 2004). Rats with neonatal lesions to the hippocampus show decreased social interaction in adolescence and adulthood, reflecting the emergence of social deficits in the premorbid stage (Sams-Dodd *et al.* 1997). The effect of DVD deficiency on social behavior in the social interaction test has been studied and no effect was observed in rats (Burne *et al.* 2004a) or mice (Harms *et al.* 2008). Lack of an effect of DVD deficiency on social interaction could indicate that the underlying pathology of social withdrawal is not related to pathways influenced by vitamin D. Alternatively, other social behaviors that have not been assessed (i.e. home cage behavior or nest building) might better capture the effects of DVD deficiency.

Mechanisms

Vitamin D has pleiotropic effects on cell differentiation and brain development in addition to its role as a neuroactive steroid (reviewed by Garcion *et al.* 2002). Animal models have been used to explore the mechanisms by which DVD deficiency can alter the brain, resulting in behavioral deficits in endophenotypes of schizophrenia. Table 2 summarizes studies aimed at identifying changes in brain circuitry, morphology and gene expression that might contribute to behavioral effects.

Glutamate

Glutamate neurotransmission, with emphasis on the NMDAR, is hypothesized to play a role in the pathophysiology of schizophrenia. This hypothesis was formulated based on the finding that administration of NMDAR antagonists such as MK-801, ketamine and phencyclidine resulted in psychosis in otherwise healthy individuals and mimicked

symptoms of schizophrenic patients (see Howes *et al.* 2015 for a review). In rodents, administration of NMDAR antagonist results in hyperlocomotion in the open field. The DVD deficiency has been shown to increase sensitivity to MK-801 in the open field in rats (Kesby *et al.* 2006, 2012; O'Loan *et al.* 2007), an effect that is blocked by haloperidol (Kesby *et al.* 2006). Increased locomotor sensitivity to MK-801 was not seen in rats whose mothers were exposed to a vitamin D-deficient diet prior to conception but not during gestation, indicating that gestation and the perinatal period constitute a critical exposure window to induce a persistent effect (O'Loan *et al.* 2007). Decreased MK-801 binding in the caudate putamen was also observed in DVD-exposed rats (Kesby *et al.* 2012), suggesting a reduction in NMDAR function. Behavioral effects in response to MK-801 were not observed in either 129 or B6J mice (Harms *et al.* 2012a). These data suggest that glutamatergic transmission through NMDARs is disrupted in rats exposed to DVD deficiency, a finding that compares to what is seen in schizophrenic patients.

Future studies are needed to assess gamma-aminobutyric acid (GABA) neurotransmission in relation to exposure to DVD deficiency. A reduction in GABA-synthesizing enzymes GAD65 and GAD67 in prefrontal cortex and hippocampus has been reported in patients with schizophrenia (reviewed in Lewis *et al.* 2012). A recent study that employed pharmacogenetic techniques (designer receptors exclusively activated by designer drugs) to specifically inhibit GABA interneurons expressing parvalbumin or GAD65 in the ventral hippocampus of mice observed hyperlocomotion and deficits in spatial working memory and PPI (Nguyen *et al.* 2014). Dysregulation of GABA transmission should be investigated as a possible mechanism linking exposure to DVD deficiency and hyperlocomotion. There is evidence that GABA transmission is dysregulated in DVD-deficient animals based on two studies that looked at gene expression in whole brain from adult rats exposed to DVD deficiency. These studies identified a decrease in expression of GABA-$A_{\alpha 4}$ (Feron *et al.* 2005) and GABA B receptor 1 (Eyles *et al.* 2007). However, other studies have reported no difference in GABA transmission (Almeras *et al.* 2007; McGrath *et al.* 2008), although the discrepancies between studies could be due to differences in brain regions analyzed. Clearly, future studies investigating the GABA system in DVD-deficient animals are warranted.

Dopamine

Schizophrenic patients show a clear dysregulation of the DA system that is thought to contribute to the emergence of positive symptoms. The presence of the VDR in dopaminergic neurons in the substantia nigra and its expression at appropriate time points during development (Cui *et al.* 2013) suggests that vitamin D can have an effect on the developing DA system in the brain.

Exposure to DVD deficiency in rodents results in dysregulation of the developing dopaminergic system in the brain. In the rat fetal mesencephalon, DVD deficiency leads to reduction of two important factors for specification of dopaminergic neurons, Nurr1 and p57Kip2 (Cui *et al.* 2010). In BALB/c mice, exposure to DVD deficiency increases gene expression of an important factor in neuronal survival and neuroprotection of dopaminergic cells (transforming growth factor $\beta 1$, *Tgf-*$\beta 1$) and a decrease in both gene and protein

expression of the DA synthesizing enzyme, tyrosine hydroxylase (*Th*), in the substantia nigra at ED17.5 (Hawes *et al.* 2015).

While it is clear the DVD deficiency disrupts the developing dopaminergic system, this effect does not appear to be as apparent in the expression of DA signaling proteins in the adult rat brain (Almeras *et al.* 2007; McGrath *et al.* 2008). However, the functioning of these proteins could be impaired without altering protein levels. A study by Kesby *et al.* (2009) found that there was a decrease in conversion of the DA metabolite 3,4-dihydroxyphenylacetic acid to homovanillic acid and a decrease in expression of the needed enzyme in this reaction, catechol-*O*-methyltransferase in the DVD-deficient neonatal rat brain (Kesby *et al.* 2009). Adult female rats exposed to DVD deficiency had increased DA transport density in the caudate putamen and increased DA affinity in the nucleus accumbens indicating that the functioning of the DA proteins was enhanced (Kesby *et al.* 2010).

Increased psychostimulant-induced DA release in the striatum has been observed in patients with schizophrenia (Breier *et al.* 1997). In rodent models, psychostimulants such as amphetamine, that induce the release of DA and increase locomotor behavior, are administered to assess functioning of the dopaminergic system. The DVD deficiency in female but not in male rats results in increased locomotor response to amphetamine in adulthood (Kesby *et al.* 2010). This finding was not observed in juvenile rats, mimicking the adult onset that is typical of schizophrenia (Kesby *et al.* 2010). Interestingly, increased sensitivity to amphetamine was not seen in DVD-exposed B6J or 129 inbred mice indicating that species-specific and possibly genetic background differences exist (Harms *et al.* 2012a). Collectively, these studies show that vitamin D deficiency during development has a significant effect on the development and functioning of the dopaminergic system and that there is a behavioral manifestation of DA dysregulation in adulthood in rats.

Maternal care

The quality of maternal care has been shown to have a consistent and appreciable effect on behavior in adult offspring (Francis *et al.* 1999; Szyf 2013) leading one to question whether maternal behavior differs among mothers exposed to vitamin D deficiency. Interestingly, a study by Burne *et al.* (2011) showed that exposure to DVD deficiency increases maternal behaviors in the rat. The DVD-deficient mothers perform more sniffing, carrying and retrieval of pups in a pup retrieval test (Burne *et al.* 2011). Pups exposed to higher levels of maternal care have previously been shown to have a lower corticosterone response to a stressor and less anxiety-like behavior in adulthood than pups of dams who exhibit low amounts of maternal behaviors (see review by Francis & Meaney 1999). Furthermore, it is thought that maternal behavior is stimulated, in part, in response to pup ultrasonic vocalizations, which are mediated by the DA system (Dastur *et al.* 1999). Since the dopaminergic system is altered by DVD deficiency (Cui *et al.* 2007, 2010; Kesby *et al.* 2009, 2010), Burne *et al.* (2011) examined the effect of DVD deficiency on calling rate of isolation-induced ultrasonic vocalizations but observed no differences.

A recent study examined the effect of exposure to DVD deficiency in BALB/c mice and reported that mothers on the vitamin D-deficient diet had significantly increased

corticosterone levels during pregnancy, indicating higher stress levels (Tesic *et al.* 2015). Tesic *et al.* also reported that the placenta of DVD-exposed mothers showed deficiencies in 11β-hydroxysteroid dehydrogenase type 11, which inactivates glucocorticoids and protects the fetus from overexposure, and an increase in a highly sensitive glucocorticoid factor (Tesic *et al.* 2015). These findings would suggest that developing pups of vitamin D-deficient BALB/c mothers are being exposed to high levels of stress hormones *in utero*. The findings of this study are in contrast to a previous study in rats that found no difference in corticosterone levels at baseline or after a restraint stress in pregnant dams exposed to a DVD-deficient diet or their male offspring in adulthood (Eyles *et al.* 2006). These conflicting results highlight the recurring finding of species differences in response to DVD deficiency and emphasize the need for future studies directed at identifying potential mechanisms.

Structural brain abnormalities

Structural brain abnormalities in patients with schizophrenia include decreased overall brain, temporal lobe and amygdala/hippocampal volume and increased lateral ventricles (reviewed by Lawrie & Abukmeil 1998). Rats exposed to DVD deficiency were also found to have enlarged lateral ventricles and a thinner cortex at birth (Eyles *et al.* 2003; Feron *et al.* 2005). However, the opposite phenotype was seen in mice. Mice exposed to DVD deficiency have smaller lateral ventricles *in utero* (Hawes *et al.* 2015) and in adulthood (Fernandes de Abreu *et al.* 2010; Harms *et al.* 2012a). The DVD deficiency also resulted in a larger striatum and smaller hippocampus in adult B6J males and a smaller hippocampus in females at birth (Fernandes de Abreu *et al.* 2010; Harms *et al.* 2012a).

Vitamin D has anti-proliferative, pro-apoptotic and differentiation properties in various cell types (Berridge 2015). Embryonic rat hippocampal neurons treated with vitamin D had a decreased percentage of cells in mitosis and increased neurite outgrowth (Brown *et al.* 2003) and mouse hippocampal neurons treated with vitamin D showed a decrease in cell proliferation and an increase in differentiation (Marini *et al.* 2010). Conversely, rats exposed to DVD deficiency exhibited an increased number of mitotic cells from gestation into the early postnatal period (Eyles *et al.* 2003; Ko *et al.* 2004), upregulation of pro-mitotic genes involved in cell cycle progression and a decrease in apoptosis and pro-apoptotic gene expression (Ko *et al.* 2004). Primary hippocampal cultures from rats exposed to DVD showed an increased number of neurospheres in the subventricular zone indicating increased activity of neural progenitor cells (Cui *et al.* 2007). Taken together, these results suggest that vitamin D plays a role in promoting healthy cellular development of the brain and a deficiency of this key regulator during brain development *in utero* can lead to brain abnormalities similar to those seen in schizophrenic patients. More research is needed to examine the differences in brain abnormalities in rats vs. mice and determine if this could explain some of the behavioral differences between the two species. If so, examination of these differences would provide insight into resilience vs. susceptibility to develop schizophrenia in those exposed to vitamin D deficiency during the perinatal period.

Neurotrophic factors

Neurotrophins such as nerve growth factor (NGF) and brain-derived neurotrophic factor (BDNF) have been implicated in the pathophysiology of schizophrenia. Nerve growth factor and BDNF are involved in promotion of neuronal growth and differentiation in the developing nervous system and synaptic plasticity throughout life. Peripheral BDNF and NGF levels are reduced in patients with schizophrenia both before and during treatment with antipsychotics (reviewed by Green *et al.* 2011; Martinotti *et al.* 2012; Weickert *et al.* 2003). However, there is some debate in the literature with regard to BDNF levels since a few studies have reported increased BDNF levels (Autry & Monteggia 2012; Martinotti *et al.* 2012). Differences between studies are thought to reflect treatment with antipsychotics, brain region and sample type (e.g. serum, whole blood and brain tissue). Regardless, there is general agreement in the literature that NGF and BDNF are dysregulated in schizophrenic patients and animal models of schizophrenia (Pillai 2008). However, a gap still exists linking neurotrophic dysregulation and manifestation of symptoms.

Vitamin D has been shown to result in NGF production *in vitro* in cultured embryonic rat hippocampal neurons (Brown *et al.* 2003). Conversely, as anticipated, exposure to DVD deficiency results in a decrease in NGF as well as glial cell line-derived neurotrophic factor and low affinity neurotrophin receptor $p75^{NTR}$ at birth (Eyles *et al.* 2003; Feron *et al.* 2005). Decreases in NGF also persist into adulthood (Eyles *et al.* 2003). Exposure to DVD deficiency also results in decreased *Bdnf* gene expression in BALB/c mice at ED14.5 but increased expression at ED17.5 compared with control animals (Hawes *et al.* 2015). A decrease in neurotrophic factors in DVD-deficient rodent models mimics what is reported in patients with schizophrenia indicating that vitamin D might play a mechanistic role in neurotrophic dysregulation. It is possible that the decrease in neurotrophic factors observed in both schizophrenics and DVD-deficient rodents might contribute to cognitive behaviors such as learning and memory where synaptic plasticity plays a major role.

Dysregulation of gene and protein expression in the brain

The ability of exposures in development to induce behavioral changes in adulthood are thought to be because of altered gene expression, possibly through epigenetic mechanisms that can persist over time (Isles 2015). Identifying genes that are altered in response to a specific manipulation (i.e. vitamin D deficiency) is challenging because of the complexity of the genome. However, detecting gene expression changes in response to vitamin D deficiency in development can provide insight into the mechanisms that result in behavioral changes in adulthood and ultimately provide targets for treatment. Whole-brain tissue from adult rats exposed to DVD deficiency showed dysregulated expression of 74 genes involved in oxidative phosphorylation, redox balance, cytoskeleton maintenance, calcium homeostasis, synaptic plasticity, neurotransmission, chaperoning and posttranslational modifications, with the majority of the genes being downregulated (Eyles *et al.* 2007). In concordance with this finding, the same study also reported dysregulation of protein expression in the same cellular processes for 17 and 23 proteins in the frontal cortex and hippocampus, respectively, and 4 proteins in both regions (Hs7C, Tbb1, EnoG and ATPb) (Almeras *et al.* 2007). Again, the majority of these proteins were found to be downregulated in adult rats exposed to DVD deficiency and were localized to mitochondria, cytoskeleton

and synapses (Almeras *et al.* 2007). A similar study examined protein expression in the nucleus accumbens and found significant downregulation of 22 proteins and upregulation of 13 proteins in rats exposed to DVD deficiency (McGrath *et al.* 2008). Dysregulated proteins in the nucleus accumbens included calcium binding, dynamin-like and mitochondrial proteins (McGrath *et al.* 2008). Of note, there was no overlap in dysregulated proteins identified in the nucleus accumbens, frontal cortex and hippocampus (Almeras *et al.* 2007; McGrath *et al.* 2008). In another study analyzing specific genes of interest via RT-PCR, exposure to a vitamin D-deficient diet in the DVD model or DVD + postnatal period resulted in decreased expression of genes involved in neuronal structure including *Gabra4*, *Map2* and *Nefl* in whole brain from adult rats (Feron *et al.* 2005).

The biological processes identified in gene and protein expression studies from schizophrenics and rodents exposed to DVD deficiency show considerable overlap. Gene expression microarray analysis of prefrontal cortex tissue from schizophrenics identified downregulation of genes involved in presynaptic function including *N*-ethylmaleimide sensitive factor (*Nsf*) and synapsin II (*Syn2*) (Mirnics *et al.* 2000). *N*-ethylmaleimide sensitive factor was also downregulated in whole brain (Eyles *et al.* 2007) and the SYN2 protein was upregulated in the frontal cortex of rats exposed to DVD deficiency (Almeras *et al.* 2007). Another study compared postmortem brain tissue of schizophrenic patients and healthy controls using proteomic and microarray analysis and found that 90% of dysregulated genes were involved in mitochondrial function, specifically energy metabolism and oxidative stress (Prabakaran *et al.* 2004). Specific proteins (capitalized) and genes (lowercase) that are dysregulated in both brain tissue from schizophrenic patients and rats exposed to DVD deficiency include those involved in neurotransmission (MAPK2, ENOG, 143G, VIS1, GAP43, SYN2, *Nsf*, *Dlgh1*, *Glul*, *Syt1*, *Cplx2* and *Gabbr1*), cytoskeleton maintenance (DREB, GFAP, *Map2*, *Kic1*, *Gfap* and *Ckb*), mitochondrial functioning (MDHC, COX6a1, ATPB, *Atpb* and *Sod2*), posttranslational modifications (PSA2, HS7C, UCHL1, *Psa2* and *Uchl1*) and the calcium-binding protein, *Ppp3r1* (Almeras *et al.* 2007; Eyles *et al.* 2007; McGrath *et al.* 2008). Apolipoprotein E (ApoE) is downregulated in hippocampal tissue from adult rats exposed to DVD deficiency and allelic differences in ApoE have also been observed in postmortem tissue from schizophrenics (Harrington *et al.* 1995).

The studies discussed above provide a platform on which to begin to unravel the pathways by which DVD deficiency is altering the genome. More research is needed to understand how vitamin D is altering expression of these genes (i.e. epigenetic changes) and if the changes induced by DVD deficiency interact with genetic background.

Conclusions and future directions

The studies discussed above highlight subtle and specific alterations in behavior and neural development that result from exposure to a diet deficient in vitamin D during critical periods of development. These studies have also begun to elucidate the complex underlying mechanisms for how exposure to a diet deficient in vitamin D in gestation can lead to persistent changes in behavior in adulthood. These findings include disruption of normal brain development, dysregulation of specific genes and protein systems and alterations of

the dopaminergic system and key neurotrophic factors. However, it is important to note that most of these studies were conducted in Sprague-Dawley rats. There are very few studies of DVD deficiency that have been conducted in mice. Mice are not necessarily a better model system than rats, but do offer some advantages in terms of tools available for genomic analysis and mechanistic studies. Importantly, there are both congruent and disparate results between studies utilizing rats vs. mice (Table 3). It should be noted that the rat studies were conducted on a genetically heterogeneous, outbred background while the mouse studies were performed in genetically homogeneous inbred strains. The observed differences between rats and mice could indicate gene by environment interactions where the effect of exposure to vitamin D deficiency in development on a specific phenotype depends on genetic background. Therefore, one future direction is to assess the effect of DVD deficiency on a genetically diverse set of rodents such as the Collaborative Cross (Churchill *et al.* 2004) that has been optimized for systems genetics studies or outbred mice (Churchill *et al.* 2012; Schmidt 2015) to more completely assess gene by environment interactions and potential causative mechanisms.

The behavioral effects of DVD exposure vary based on the behavioral assessment used (i.e. hyperlocomotion in various assays and diverse learning tasks). Furthermore, the behavioral effects observed in rats were not always replicable even within the same laboratory, indicating that the behavioral effects of DVD deficiency may be unstable or sensitive to subtle differences in the environment. This is particularly important based on our observation that the majority of the literature on DVD deficiency has come from the same research group at The University of Queensland in Australia. Although this group has carried out a thorough job characterizing numerous behavioral phenotypes and the underlying mechanisms responsible for persistent changes in behavior, there is a need for additional studies by other groups to determine if these subtle behavioral phenotypes can be reproduced.

Collectively, we can conclude that exposure to a diet deficient in vitamin D during development can lead to subtle behavioral changes in adulthood and that these changes are dependent on the timing of the exposure, the model system (rats vs. mice) and genetic background.

These studies highlight the potential importance of monitoring vitamin D levels in pregnant women. The World Health Organization released a report in 2012 and concluded that vitamin D supplementation was not recommended for pregnant women as part of the standard of care (World Health Organization, 2012). However, the effects of *in utero* exposure to low vitamin D on mental health in adulthood were not considered. More work needs to be carried out in this area if we are to truly understand the role of vitamin D deficiency in schizophrenia and gain a better understanding of the neurobiological systems that are affected and increase risk for this devastating disease.

References

Almeras L, Eyles D, Benech P, Laffite D, Villard C, Patatian A, Boucraut J, Mackay-Sim A, McGrath J, Feron F. Developmental vitamin D deficiency alters brain protein expression in the adult rat: implications for neuropsychiatric disorders. Proteomics. 2007; 7:769–780. [PubMed: 17295352]

Altemus KL, Finger S, Wolf C, Birge SJ. Behavioral correlates of vitamin D deficiency. Physiol Behav. 1987; 39:435–440. [PubMed: 3575489]

Amitai N, Semenova S, Markou A. Clozapine attenuates disruptions in response inhibition and task efficiency induced by repeated phencyclidine administration in the intracranial self-stimulation procedure. Eur J Pharmacol. 2009; 602:78–84. [PubMed: 19026629]

Anstrom, Woodward. Restraint increases dopaminergic burst firing in awake rats. Neuropsychopharmacology. 2005; 30:1832–1840. [PubMed: 15886724]

Arguello PA, Gogos JA. Cognition in mouse models of schizophrenia susceptibility genes. Schizophr Bull. 2010; 36:289–300. [PubMed: 20026558]

Audet MC, Goulet S, Dore FY. Repeated subchronic exposure to phencyclidine elicits excessive atypical grooming in rats. Behav Brain Res. 2006; 167:103–110. [PubMed: 16257455]

Autry AE, Monteggia LM. Brain-derived neurotrophic factor and neuropsychiatric disorders. Pharmacol Rev. 2012; 64:238–258. [PubMed: 22407616]

Babenko O, Kovalchuk I, Metz GA. Stress-induced perinatal and transgenerational epigenetic programming of brain development and mental health. Neurosci Biobehav Rev. 2015; 48:70–91. [PubMed: 25464029]

Barnes CA. Memory deficits associated with senescence: a neurophysiological and behavioral study in the rat. J Comp Physiol Psychol. 1979; 93:74–104. [PubMed: 221551]

Becker A, Grecksch G. Pharmacological treatment to augment hole board habituation in prenatal vitamin D-deficient rats. Behav Brain Res. 2006; 166:177–183. [PubMed: 16188330]

Becker A, Eyles DW, McGrath JJ, Grecksch G. Transient prenatal vitamin D deficiency is associated with subtle alterations in learning and memory functions in adult rats. Behav Brain Res. 2005; 161:306–312. [PubMed: 15922058]

Belforte JE, Zsiros V, Sklar ER, Jiang Z, Yu G, Li Y, Quinlan EM, Nakazawa K. Postnatal NMDA receptor ablation in corticolimbic interneurons confers schizophrenia-like phenotypes. Nat Neurosci. 2010; 13:76–83. [PubMed: 19915563]

Bergeron SA, Carrier N, Li GH, Ahn S, Burgess HA. Gsx1 expression defines neurons required for prepulse inhibition. Mol Psychiatry. 2015; 20:974–985. [PubMed: 25224259]

Berlin I, Givry-Steiner L, Lecrubier Y, Puech AJ. Measures of anhedonia and hedonic responses to sucrose in depressive and schizophrenic patients in comparison with healthy subjects. Eur Psychiatry. 1998; 13:303–309. [PubMed: 19698645]

Berridge MJ. Vitamin D cell signalling in health and disease. Biochem Biophys Res Commun. 2015; 460:53–71. [PubMed: 25998734]

Birrell JM, Brown VJ. Medial frontal cortex mediates perceptual attentional set shifting in the rat. J Neurosci. 2000; 20:4320–4324. [PubMed: 10818167]

Black MD, Lister S, Hitchcock JM, Van Giersbergen P, Sorensen SM. Neonatal hippocampal lesion model of schizophrenia in rats: sex differences and persistence of effects into maturity. Drug Dev Res. 1998; 43:206–213.

Borsini F, Lecci A, Volterra G, Meli A. A model to measure anticipatory anxiety in mice? Psychopharmacology (Berl). 1989; 98:207–211. [PubMed: 2502791]

Braff DL, Grillon C, Geyer MA. Gating and habituation of the startle reflex in schizophrenic patients. Arch Gen Psychiatry. 1992; 49:206–215. [PubMed: 1567275]

Braff DL, Geyer MA, Swerdlow NR. Human studies of prepulse inhibition of startle: normal subjects, patient groups, and pharmacological studies. Psychopharmacology (Berl). 2001; 156:234–258. [PubMed: 11549226]

Breier A, Su TP, Saunders R, Carson RE, Kolachana BS, de Bartolomeis A, Weinberger DR, Weisenfeld N, Malhotra AK, Eckelman WC, Pickar D. Schizophrenia is associated with elevated amphetamine-induced synaptic dopamine concentrations: evidence from a novel positron emission tomography method. Proc Natl Acad Sci U S A. 1997; 94:2569–2574. [PubMed: 9122236]

Brown AS. The environment and susceptibility to schizophrenia. Prog Neurobiol. 2011; 93:23–58. [PubMed: 20955757]

Brown J, Bianco JI, McGrath JJ, Eyles DW. 1,25-Dihydroxyvitamin D3 induces nerve growth factor, promotes neurite outgrowth and inhibits mitosis in embryonic rat hippocampal neurons. Neurosci Lett. 2003; 343:139–143. [PubMed: 12759183]

Burkert R, McGrath J, Eyles D. Vitamin D receptor expression in the embryonic rat brain. Neurosci Res Commun. 2003; 33:63071.

Burne TH, Becker A, Brown J, Eyles DW, Mackay-Sim A, McGrath JJ. Transient prenatal vitamin D deficiency is associated with hyperlocomotion in adult rats. Behav Brain Res. 2004a; 154:549–555. [PubMed: 15313044]

Burne TH, Feron F, Brown J, Eyles DW, McGrath JJ, Mackay-Sim A. Combined prenatal and chronic postnatal vitamin D deficiency in rats impairs prepulse inhibition of acoustic startle. Physiol Behav. 2004b; 81:651–655. [PubMed: 15178159]

Burne TH, O'Loan J, McGrath JJ, Eyles DW. Hyperlocomotion associated with transient prenatal vitamin D deficiency is ameliorated by acute restraint. Behav Brain Res. 2006; 174:119–124. [PubMed: 16930734]

Burne TH, O'Loan J, Splatt K, Alexander S, McGrath JJ, Eyles DW. Developmental vitamin D (DVD) deficiency alters pup-retrieval but not isolation-induced pup ultrasonic vocalizations in the rat. Physiol Behav. 2011; 102:201–204. [PubMed: 21059363]

Burne TH, Alexander S, Turner KM, Eyles DW, McGrath JJ. Developmentally vitamin D-deficient rats show enhanced prepulse inhibition after acute delta9-tetrahydrocannabinol. Behav Pharmacol. 2014; 25:236–244. [PubMed: 24776491]

van den Buuse M, Garner B, Gogos A, Kusljic S. Importance of animal models in schizophrenia research. Aust N Z J Psychiatry. 2005; 39:550–557. [PubMed: 15996135]

Cantor-Graae E, Selten JP. Schizophrenia and migration: a meta-analysis and review. Am J Psychiatry. 2005; 162:12–24. [PubMed: 15625195]

Carlberg C. Genome-wide (over)view on the actions of vitamin D. Front Physiol. 2014; 5:167. [PubMed: 24808867]

Chen G, Chen KS, Knox J, Inglis J, Bernard A, Martin SJ, Justice A, McConlogue L, Games D, Freedman SB, Morris RG. A learning deficit related to age and beta-amyloid plaques in a mouse model of Alzheimer's disease. Nature. 2000; 408:975–979. [PubMed: 11140684]

Churchill GA, Airey DC, Allayee H, et al. The Collaborative Cross, a community resource for the genetic analysis of complex traits. Nat Genet. 2004; 36:1133–1137. [PubMed: 15514660]

Churchill GA, Gatti DM, Munger SC, Svenson KL. The diversity outbred mouse population. Mamm Genome. 2012; 23:713–718. [PubMed: 22892839]

Cohrs S. Sleep disturbances in patients with schizophrenia : impact and effect of antipsychotics. CNS Drugs. 2008; 22:939–962. [PubMed: 18840034]

Colacicco G, Welzl H, Lipp HP, Wurbel H. Attentional set-shifting in mice: modification of a rat paradigm, and evidence for strain-dependent variation. Behav Brain Res. 2002; 132:95–102. [PubMed: 11853862]

Connolly PM, Maxwell CR, Kanes SJ, Abel T, Liang Y, Tokarczyk J, Bilker WB, Turetsky BI, Gur RE, Siegel SJ. Inhibition of auditory evoked potentials and prepulse inhibition of startle in DBA/2J and DBA/2Hsd inbred mouse substrains. Brain Res. 2003; 992:85–95. [PubMed: 14604776]

Crawley JN. Neuropharmacologic specificity of a simple animal model for the behavioral actions of benzodiazepines. Pharmacol Biochem Behav. 1981; 15:695–699. [PubMed: 6118883]

Cross-Disorder Group of the Psychiatric Genomics Consortium. Identification of risk loci with shared effects on five major psychiatric disorders: a genome-wide analysis. Lancet. 2013; 381:1371–1379. [PubMed: 23453885]

Cross-Disorder Group of the Psychiatric Genomics Consortium. Lee SH, Ripke S, et al. Genetic relationship between five psychiatric disorders estimated from genome-wide SNPs. Nat Genet. 2013; 45:984–994. [PubMed: 23933821]

Cui X, McGrath JJ, Burne TH, Mackay-Sim A, Eyles DW. Maternal vitamin D depletion alters neurogenesis in the developing rat brain. Int J Dev Neurosci. 2007; 25:227–232. [PubMed: 17467223]

Cui X, Pelekanos M, Burne TH, McGrath JJ, Eyles DW. Maternal vitamin D deficiency alters the expression of genes involved in dopamine specification in the developing rat mesencephalon. Neurosci Lett. 2010; 486:220–223. [PubMed: 20884326]

Cui X, Pelekanos M, Liu PY, Burne TH, McGrath JJ, Eyles DW. The vitamin D receptor in dopamine neurons; its presence in human substantia nigra and its ontogenesis in rat midbrain. Neuroscience. 2013; 236:77–87. [PubMed: 23352937]

Dastur FN, McGregor IS, Brown RE. Dopaminergic modulation of rat pup ultrasonic vocalizations. Eur J Pharmacol. 1999; 382:53–67. [PubMed: 10528139]

Davies G, Welham J, Chant D, Torrey EF, McGrath J. A systematic review and meta-analysis of Northern Hemisphere season of birth studies in schizophrenia. Schizophr Bull. 2003; 29:587–593. [PubMed: 14609251]

Dere E, Huston JP, De Souza Silva MA. The pharmacology, neuroanatomy and neurogenetics of one-trial object recognition in rodents. Neurosci Biobehav Rev. 2007; 31:673–704. [PubMed: 17368764]

Di Matteo V, Di Giovanni G, Pierucci M, Esposito E. Serotonin control of central dopaminergic function: focus on in vivo microdialysis studies. Prog Brain Res. 2008; 172:7–44. [PubMed: 18772026]

Dudchenko PA, Talpos J, Young J, Baxter MG. Animal models of working memory: a review of tasks that might be used in screening drug treatments for the memory impairments found in schizophrenia. Neurosci Biobehav Rev. 2013; 37:2111–2124. [PubMed: 22464948]

Dzirasa K, Ribeiro S, Costa R, Santos LM, Lin SC, Grosmark A, Sotnikova TD, Gainetdinov RR, Caron MG, Nicolelis MA. Dopaminergic control of sleep-wake states. J Neurosci. 2006; 26:10577–10589. [PubMed: 17035544]

Ellenbroek BA, Cools AR. Apomorphine susceptibility and animal models for psychopathology: genes and environment. Behav Genet. 2002; 32:349–361. [PubMed: 12405516]

Ennaceur A, Delacour J. A new one-trial test for neurobiological studies of memory in rats. 1: behavioral data. Behav Brain Res. 1988; 31:47–59. [PubMed: 3228475]

Eyles D, Brown J, Mackay-Sim A, McGrath J, Feron F. Vitamin D3 and brain development. Neuroscience. 2003; 118:641–653. [PubMed: 12710973]

Eyles DW, Smith S, Kinobe R, Hewison M, McGrath JJ. Distribution of the vitamin D receptor and 1 alpha-hydroxylase in human brain. J Chem Neuroanat. 2005; 29:21–30. [PubMed: 15589699]

Eyles DW, Rogers F, Buller K, McGrath JJ, Ko P, French K, Burne TH. Developmental vitamin D (DVD) deficiency in the rat alters adult behaviour independently of HPA function. Psychoneuroendocrinology. 2006; 31:958–964. [PubMed: 16890375]

Eyles D, Almeras L, Benech P, Patatian A, Mackay-Sim A, McGrath J, Feron F. Developmental vitamin D deficiency alters the expression of genes encoding mitochondrial, cytoskeletal and synaptic proteins in the adult rat brain. J Steroid Biochem Mol Biol. 2007; 103:538–545. [PubMed: 17293106]

Eyles DW, Burne TH, McGrath JJ. Vitamin D, effects on brain development, adult brain function and the links between low levels of vitamin D and neuropsychiatric disease. Front Neuroendocrinol. 2013; 34:47–64. [PubMed: 22796576]

Farrow TF, Hunter MD, Haque R, Spence SA. Modafinil and unconstrained motor activity in schizophrenia: double-blind crossover placebo-controlled trial. Br J Psychiatry. 2006; 189:461–462. [PubMed: 17077439]

Feldon J, Weiner I. The latent inhibition model of schizophrenic attention disorder. Haloperidol and sulpiride enhance rats' ability to ignore irrelevant stimuli. Biol Psychiatry. 1991; 29:635–646. [PubMed: 2054435]

Ferguson JN, Young LJ, Insel TR. The neuroendocrine basis of social recognition. Front Neuroendocrinol. 2002; 23:200–224. [PubMed: 11950245]

Fernandes de Abreu DA, Nivet E, Baril N, Khrestchatisky M, Roman F, Feron F. Developmental vitamin D deficiency alters learning in C57Bl/6J mice. Behav Brain Res. 2010; 208:603–608. [PubMed: 20079764]

Feron F, Burne TH, Brown J, Smith E, McGrath JJ, Mackay-Sim A, Eyles DW. Developmental Vitamin D3 deficiency alters the adult rat brain. Brain Res Bull. 2005; 65:141–148. [PubMed: 15763180]

File; Wardill. 1975.

Francis DD, Meaney MJ. Maternal care and the development of stress responses. Curr Opin Neurobiol. 1999; 9:128–134. [PubMed: 10072372]

Francis DD, Champagne FA, Liu D, Meaney MJ. Maternal care, gene expression, and the development of individual differences in stress reactivity. Ann N Y Acad Sci. 1999; 896:66–84. [PubMed: 10681889]

Garcion E, Wion-Barbot N, Montero-Menei CN, Berger F, Wion D. New clues about vitamin D functions in the nervous system. Trends Endocrinol Metab. 2002; 13:100–105. [PubMed: 11893522]

Gardner CR, Piper DC. Effects of agents which enhance GABA-mediated neurotransmission on licking conflict in rats and exploration in mice. Eur J Pharmacol. 1982; 83:25–33. [PubMed: 6290245]

Geyer MA, Braff DL. Habituation of the Blink reflex in normals and schizophrenic patients. Psychophysiology. 1982; 19:1–6. [PubMed: 7058230]

Geyer MA, Krebs-Thomson K, Braff DL, Swerdlow NR. Pharmacological studies of prepulse inhibition models of sensorimotor gating deficits in schizophrenia: a decade in review. Psychopharmacology (Berl). 2001; 156:117–154. [PubMed: 11549216]

Grecksch G, Bernstein HG, Becker A, Hollt V, Bogerts B. Disruption of latent inhibition in rats with postnatal hippocampal lesions. Neuropsychopharmacology. 1999; 20:525–532. [PubMed: 10327422]

Green MF. What are the functional consequences of neurocognitive deficits in schizophrenia? Am J Psychiatry. 1996; 153:321–330. [PubMed: 8610818]

Green MF, Kern RS, Heaton RK. Longitudinal studies of cognition and functional outcome in schizophrenia: implications for MATRICS. Schizophr Res. 2004; 72:41–51. [PubMed: 15531406]

Green MJ, Matheson SL, Shepherd A, Weickert CS, Carr VJ. Brain-derived neurotrophic factor levels in schizophrenia: a systematic review with meta-analysis. Mol Psychiatry. 2011; 16:960–972. [PubMed: 20733577]

Harms LR, Eyles DW, McGrath JJ, Mackay-Sim A, Burne TH. Developmental vitamin D deficiency alters adult behaviour in 129/SvJ and C57BL/6J mice. Behav Brain Res. 2008; 187:343–350. [PubMed: 17996959]

Harms LR, Cowin G, Eyles DW, Kurniawan ND, McGrath JJ, Burne TH. Neuroanatomy and psychomimetic-induced locomotion in C57BL/6J and 129/X1SvJ mice exposed to developmental vitamin D deficiency. Behav Brain Res. 2012a; 230:125–131. [PubMed: 22343129]

Harms LR, Turner KM, Eyles DW, Young JW, McGrath JJ, Burne TH. Attentional processing in C57BL/6J mice exposed to developmental vitamin D deficiency. PLoS One. 2012b; 7:e35896. [PubMed: 22563415]

Harrington CR, Roth M, Xuereb JH, McKenna PJ, Wischik CM. Apolipoprotein E type epsilon 4 allele frequency is increased in patients with schizophrenia. Neurosci Lett. 1995; 202:101–104. [PubMed: 8787841]

Hawes JE, Tesic D, Whitehouse AJ, Zosky GR, Smith JT, Wyrwoll CS. Maternal vitamin D deficiency alters fetal brain development in the BALB/c mouse. Behav Brain Res. 2015; 286:192–200. [PubMed: 25753408]

Hess AF, Unger LJ. Cure of infantile rickets by sunlight. J Am Med Assoc. 1921; 77:39.

Holick MF. The vitamin D deficiency pandemic and consequences for nonskeletal health: mechanisms of action. Mol Aspects Med. 2008; 29:361–368. [PubMed: 18801384]

Holick, MF.; MacLaughlin, JA.; Parrish, JA.; Anderson, RR. The photochemistry and photobiology of vitamin D3.. In: Regan, JD.; Parrish, JA., editors. The Science of Photomedicine. Plenum; New York, NY: 1982. p. 195-218.

Howes O, McCutcheon R, Stone J. Glutamate and dopamine in schizophrenia: an update for the 21st century. J Psychopharmacol. 2015; 29:97–115. [PubMed: 25586400]

Isles AR. Neural and behavioral epigenetics; what it is, and what is hype. Genes Brain Behav. 2015; 14:64–72. [PubMed: 25346298]

Kellendonk C, Simpson EH, Kandel ER. Modeling cognitive endophenotypes of schizophrenia in mice. Trends Neurosci. 2009; 32:347–358. [PubMed: 19409625]

Kendler KS. Twin studies of psychiatric illness: an update. Arch Gen Psychiatry. 2001; 58:1005–1014. [PubMed: 11695946]

Kesby JP, Burne TH, McGrath JJ, Eyles DW. Developmental vitamin D deficiency alters MK 801-induced hyperlocomotion in the adult rat: an animal model of schizophrenia. Biol Psychiatry. 2006; 60:591–596. [PubMed: 16697353]

Kesby JP, Cui X, Ko P, McGrath JJ, Burne TH, Eyles DW. Developmental vitamin D deficiency alters dopamine turnover in neonatal rat forebrain. Neurosci Lett. 2009; 461:155–158. [PubMed: 19500655]

Kesby JP, Cui X, O'Loan J, McGrath JJ, Burne TH, Eyles DW. Developmental vitamin D deficiency alters dopamine-mediated behaviors and dopamine transporter function in adult female rats. Psychopharmacology (Berl). 2010; 208:159–168. [PubMed: 19921153]

Kesby JP, O'Loan JC, Alexander S, Deng C, Huang XF, McGrath JJ, Eyles DW, Burne TH. Developmental vitamin D deficiency alters MK-801-induced behaviours in adult offspring. Psychopharmacology (Berl). 2012; 220:455–463. [PubMed: 21947313]

Kesby JP, Cui X, Burne TH, Eyles DW. Altered dopamine ontogeny in the developmentally vitamin D deficient rat and its relevance to schizophrenia. Front Cell Neurosci. 2013; 7:111. [PubMed: 23882183]

Knuesel I, Chicha L, Britschgi M, Schobel SA, Bodmer M, Hellings JA, Toovey S, Prinssen EP. Maternal immune activation and abnormal brain development across CNS disorders. Nat Rev Neurol. 2014; 10:643–660. [PubMed: 25311587]

Ko P, Burkert R, McGrath J, Eyles D. Maternal vitamin D3 deprivation and the regulation of apoptosis and cell cycle during rat brain development. Brain Res Dev Brain Res. 2004; 153:61–68. [PubMed: 15464218]

Lawrie SM, Abukmeil SS. Brain abnormality in schizophrenia. A systematic and quantitative review of volumetric magnetic resonance imaging studies. Br J Psychiatry. 1998; 172:110–120. [PubMed: 9519062]

Le Pen G, Gaudet L, Mortas P, Mory R, Moreau JL. Deficits in reward sensitivity in a neurodevelopmental rat model of schizophrenia. Psychopharmacology (Berl). 2002; 161:434–441. [PubMed: 12073172]

Lee J, Park S. Working memory impairments in schizophrenia: a meta-analysis. J Abnorm Psychol. 2005; 114:599–611. [PubMed: 16351383]

Levin ED, Kim P, Meray R. Chronic nicotine working and reference memory effects in the 16-arm radial maze: interactions with D1 agonist and antagonist drugs. Psychopharmacology (Berl). 1996; 127:25–30. [PubMed: 8880940]

Lewis DA, Curley AA, Glausier JR, Volk DW. Cortical parvalbumin interneurons and cognitive dysfunction in schizophrenia. Trends Neurosci. 2012; 35:57–67. [PubMed: 22154068]

Lodge DJ, Grace AA. Hippocampal dysfunction and disruption of dopamine system regulation in an animal model of schizophrenia. Neurotox Res. 2008; 14:97–104. [PubMed: 19073417]

Lubow RE, Gewirtz JC. Latent inhibition in humans: data, theory, and implications for schizophrenia. Psychol Bull. 1995; 117:87–103. [PubMed: 7870865]

March D, Hatch SL, Morgan C, Kirkbride JB, Bresnahan M, Fearon P, Susser E. Psychosis and place. Epidemiol Rev. 2008; 30:84–100. [PubMed: 18669521]

Marini F, Bartoccini E, Cascianelli G, Voccoli V, Baviglia MG, Magni MV, Garcia-Gil M, Albi E. Effect of 1alpha,25-dihydroxyvitamin D3 in embryonic hippocampal cells. Hippocampus. 2010; 20:696–705. [PubMed: 19603526]

Martinotti G, Di Iorio G, Marini S, Ricci V, De Berardis D, Di Giannantonio M. Nerve growth factor and brain-derived neurotrophic factor concentrations in schizophrenia: a review. J Biol Regul Homeost Agents. 2012; 26:347–356. [PubMed: 23034254]

McGrath J. Hypothesis: is low prenatal vitamin D a risk-modifying factor for schizophrenia? Schizophr Res. 1999; 40:173–177. [PubMed: 10638855]

McGrath J. Does ‘imprinting’ with low prenatal vitamin D contribute to the risk of various adult disorders? Med Hypotheses. 2001; 56:367–371. [PubMed: 11359362]

McGrath JJ. The surprisingly rich contours of schizophrenia epidemiology. Arch Gen Psychiatry. 2007; 64:14–16. [PubMed: 17199050]

McGrath J, Iwazaki T, Eyles D, Burne T, Cui X, Ko P, Matsumoto I. Protein expression in the nucleus accumbens of rats exposed to developmental vitamin D deficiency. PLoS One. 2008; 3:e2383. [PubMed: 18545652]

Mirnics K, Middleton FA, Marquez A, Lewis DA, Levitt P. Molecular characterization of schizophrenia viewed by microarray analysis of gene expression in prefrontal cortex. Neuron. 2000; 28:53–67. [PubMed: 11086983]

Mongeau R, Marcello S, Andersen JS, Pani L. Contrasting effects of diazepam and repeated restraint stress on latent inhibition in mice. Behav Brain Res. 2007; 183:147–155. [PubMed: 17629580]

Morris RGM. Spatial localization does not require the presence of local cues. Learn Motiv. 1981; 12:239–260.

Nadler JJ, Moy SS, Dold G, Trang D, Simmons N, Perez A, Young NB, Barbaro RP, Piven J, Magnuson TR, Crawley JN. Automated apparatus for quantitation of social approach behaviors in mice. Genes Brain Behav. 2004; 3:303–314. [PubMed: 15344923]

Network & Pathway Analysis Subgroup of Psychiatric Genomics Consortium. Psychiatric genome-wide association study analyses implicate neuronal, immune and histone pathways. Nat Neurosci. 2015; 18:199–209. [PubMed: 25599223]

Nguyen R, Morrissey MD, Mahadevan V, Cajanding JD, Woodin MA, Yeomans JS, Takehara-Nishiuchi K, Kim JC. Parvalbumin and GAD65 interneuron inhibition in the ventral hippocampus induces distinct behavioral deficits relevant to schizophrenia. J Neurosci. 2014; 34:14948–14960. [PubMed: 25378161]

Njung'e K, Handley SL. Evaluation of marble-burying behavior as a model of anxiety. Pharmacol Biochem Behav. 1991; 38:63–67. [PubMed: 2017455]

O'Loan J, Eyles DW, Kesby J, Ko P, McGrath JJ, Burne TH. Vitamin D deficiency during various stages of pregnancy in the rat; its impact on development and behaviour in adult offspring. Psychoneuroendocrinology. 2007; 32:227–234. [PubMed: 17276604]

Pan P, Jin DH, Chatterjee-Chakraborty M, Halievski K, Lawson D, Remedios D, Smetka C, Pinto V, Parra E, Fleming AS. The effects of vitamin D(3) during pregnancy and lactation on offspring physiology and behavior in Sprague-Dawley rats. Dev Psychobiol. 2014; 56:12–22. [PubMed: 23129442]

Paylor R, Zhao Y, Libbey M, Westphal H, Crawley JN. Learning impairments and motor dysfunctions in adult Lhx5-deficient mice displaying hippocampal disorganization. Physiol Behav. 2001; 73:781–792. [PubMed: 11566211]

Peak JN, Turner KM, Burne TH. The effect of developmental vitamin D deficiency in male and female Sprague-Dawley rats on decision-making using a rodent gambling task. Physiol Behav. 2015; 138:319–324. [PubMed: 25447469]

Pillai A. Brain-derived neurotropic factor/TrkB signaling in the pathogenesis and novel pharmacotherapy of schizophrenia. Neurosignals. 2008; 16:183–193. [PubMed: 18253057]

Porsolt RD, Le Pichon M, Jalfre M. Depression: a new animal model sensitive to antidepressant treatments. Nature. 1977; 266:730–732. [PubMed: 559941]

Prabakaran S, Swatton JE, Ryan MM, Huffaker SJ, Huang JTJ, Griffin JL, Wayland M, Freeman T, Dudbridge F, Lilley KS, Karp NA, Hester S, Tkachev D, Mimmack ML, Yolken RH, Webster MJ, Torrey EF, Bahn S. Mitochondrial dysfunction in schizophrenia: evidence for compromised brain metabolism and oxidative stress. Mol Psychiatry. 2004; 9:684–697. [PubMed: 15098003]

Prut L, Belzung C. The open field as a paradigm to measure the effects of drugs on anxiety-like behaviors: a review. Eur J Pharmacol. 2003; 463:3–33. [PubMed: 12600700]

Ragozzino ME, Wilcox C, Raso M, Kesner RP. Involvement of rodent prefrontal cortex subregions in strategy switching. Behav Neurosci. 1999; 113:32–41. [PubMed: 10197904]

Ripke S, O'Dushlaine C, Chambert K, et al. Genome-wide association analysis identifies 13 new risk loci for schizophrenia. Nat Genet. 2013; 45:1150–1159. [PubMed: 23974872]

Robbins TW. The 5-choice serial reaction time task: behavioural pharmacology and functional neurochemistry. Psychopharmacology (Berl). 2002; 163:362–380. [PubMed: 12373437]

Rodgers RJ, Johnson NJ. Factor analysis of spatiotemporal and ethological measures in the murine elevated plus-maze test of anxiety. Pharmacol Biochem Behav. 1995; 52:297–303. [PubMed: 8577794]

Ryan JW, Anderson PH, Morris HA. Pleiotropic activities of vitamin d receptors - adequate activation for multiple health outcomes. Clin Biochem Rev. 2015; 36:53–61. [PubMed: 26224895]

Sams-Dodd F, Lipska BK, Weinberger DR. Neonatal lesions of the rat ventral hippocampus result in hyperlocomotion and deficits in social behaviour in adulthood. Psychopharmacology (Berl). 1997; 132:303–310. [PubMed: 9292631]

Schmidt CW. Diversity outbred: a new generation of mouse model. Environ Health Perspect. 2015; 123:A64–A67. [PubMed: 25730842]

Seligman ME, Beagley G. Learned helplessness in the rat. J Comp Physiol Psychol. 1975; 88:534–541. [PubMed: 1150935]

Slotnick B. Animal cognition and the rat olfactory system. Trends Cogn Sci. 2001; 5:216–222. [PubMed: 11323267]

Steru L, Chermat R, Thierry B, Simon P. The tail suspension test: a new method for screening antidepressants in mice. Psychopharmacology (Berl). 1985; 85:367–370. [PubMed: 3923523]

Substance Abuse and Mental Health Services Administration. Results from the 2013 National Survey on Drug Use and Health: Mental Health Findings. Substance Abuse and Mental Health Services Administration; Rockville, MD: 2014.

Sullivan PF. Genetics of disease: associations with depression. Nature. 2015; 523:539–540. [PubMed: 26176922]

Szyf M. DNA methylation, behavior and early life adversity. J Genet Genomics = Yi Chuan Xue Bao. 2013; 40:331–338. [PubMed: 23876773]

Tarantino, LM.; Reyes, TM.; Palmer, AA. Animal models of prenatal protein malnutrition relevant for schizophrenia.. In: Brown, AS.; Patterson, PH., editors. The Origins of Schizophrenia. Columbia University Press; New York, NY: 2012. p. 300-334.

Tesic D, Hawes JE, Zosky GR, Wyrwoll CS. Vitamin D deficiency in BALB/c mouse pregnancy increases placental transfer of glucocorticoids. Endocrinology. 2015; 156:3673–3679. [PubMed: 26252062]

Torres G, Meeder BA, Hallas BH, Gross KW, Horowitz JM. Preliminary evidence for reduced social interactions in Chakragati mutants modeling certain symptoms of schizophrenia. Brain Res. 2005; 1046:180–186. [PubMed: 15882844]

Torrey EF, Miller J, Rawlings R, Yolken RH. Seasonality of births in schizophrenia and bipolar disorder: a review of the literature. Schizophr Res. 1997; 28:1–38. [PubMed: 9428062]

Turner KM, Young JW, McGrath JJ, Eyles DW, Burne TH. Cognitive performance and response inhibition in developmentally vitamin D (DVD)-deficient rats. Behav Brain Res. 2013; 242:47–53. [PubMed: 23275047]

Uchida N, Mainen ZF. Speed and accuracy of olfactory discrimination in the rat. Nat Neurosci. 2003; 6:1224–1229. [PubMed: 14566341]

Umbricht D, Vyssotki D, Latanov A, Nitsch R, Lipp HP. Deviance-related electrophysiological activity in mice: is there mismatch negativity in mice? Clin Neurophysiol. 2005; 116:353–363. [PubMed: 15661113]

Vingerhoets WA, Bloemen OJ, Bakker G, van Amelsvoort TA. Pharmacological interventions for the MATRICS cognitive domains in schizophrenia: what's the evidence? Front Psychiatry. 2013; 4:157. [PubMed: 24363646]

Webb AR, Holick MF. The role of sunlight in the cutaneous production of vitamin D3. Annu Rev Nutr. 1988; 8:375–399. [PubMed: 2849469]

Weickert CS, Hyde TM, Lipska BK, Herman MM, Weinberger DR, Kleinman JE. Reduced brain-derived neurotrophic factor in prefrontal cortex of patients with schizophrenia. Mol Psychiatry. 2003; 8:592–610. [PubMed: 12851636]

Widholm JJ, Clarkson GB, Strupp BJ, Crofton KM, Seegal RF, Schantz SL. Spatial reversal learning in Aroclor 1254-exposed rats: sex-specific deficits in associative ability and inhibitory control. Toxicol Appl Pharmacol. 2001; 174:188–198. [PubMed: 11446834]

Wiley JL, Compton AD. Progressive ratio performance following challenge with antipsychotics, amphetamine, or NMDA antagonists in adult rats treated perinatally with phencyclidine. Psychopharmacology (Berl). 2004; 177:170–177. [PubMed: 15243736]

Wilson CA, Koenig JI. Social interaction and social withdrawal in rodents as readouts for investigating the negative symptoms of schizophrenia. Eur Neuropsychopharmacol. 2014; 24:759–773. [PubMed: 24342774]

World Health Organization. Guideline: Vitamin D Supplementation in Pregnant Women. World Health Organization, Geneva: 2012.

Young JW, Minassian A, Paulus MP, Geyer MA, Perry W. A reverse-translational approach to bipolar disorder: rodent and human studies in the behavioral pattern monitor. Neurosci Biobehav Rev. 2007; 31:882–896. [PubMed: 17706782]

Young JW, Light GA, Marston HM, Sharp R, Geyer MA. The 5-choice continuous performance test: evidence for a translational test of vigilance for mice. PLoS One. 2009a; 4:e4227. [PubMed: 19156216]

Young JW, Powell SB, Risbrough V, Marston HM, Geyer MA. Using the MATRICS to guide development of a preclinical cognitive test battery for research in schizophrenia. Pharmacol Ther. 2009b; 122:150–202. [PubMed: 19269307]

Zeeb FD, Robbins TW, Winstanley CA. Serotonergic and dopaminergic modulation of gambling behavior as assessed using a novel rat gambling task. Neuropsychopharmacology. 2009; 34:2329–2343. [PubMed: 19536111]

Table 1

Commonly used animal models to measure schizophrenia endophenotypes

	Human correlate	Animal model	References
Positive	Psychomotor agitation	Locomotor activity and response to novelty	Farrow *et al.* (2006); Young *et al.* (2007)
	Disorganized behavior	Patterns of locomotor activity	Young *et al.* (2007)
Negative	Anhedonia	Saccharine or sucrose consumption, intracranial self-stimulation	Amitai *et al.* (2009); Berlin *et al.* (1998); Le Pen *et al.* (2002)
	Avolition (lack of motivation)	Progressive ratio, conditioning paradigms	Wiley and Compton (2004)
	Social withdrawal	Social interaction	Nadler *et al.* (2004)
		Resident intruder	Ellenbroek and Cools (2002)
		Nest building	Belforte *et al.* (2010)
		Home cage social behavior	Torres *et al.* (2005)
Cognitive	Working memory	T-maze, holeboard, radial arm maze	File and Wardill (1975); Levin *et al.* (1996)
	Visual learning and memory	Morris water maze, novel object recognition, Barnes maze	Barnes (1979); Chen *et al.* (2000); Dere *et al.* (2007); Ennaceur and Delacour (1988); Morris (1981); Paylor *et al.* (2001)
	Reasoning/problem solving	Attentional set shifting; cross-maze-set-shifting task; serial reversal acquisition paradigm, rodent gambling task	Birrell and Brown (2000); Colacicco *et al.* (2002); Ragozzino *et al.* (1999); Widholm *et al.* (2001); Zeeb *et al.* (2009)
	Attention/vigilance	5C-SRT 5C-CPT	Robbins (2002); Young *et al.* (2009a)
	Processing speed	5C-SRT 5C-CPT, olfactory discrimination	Slotnick (2001); Uchida and Mainen (2003)
	Social cognition	Social interaction or recognition	Ferguson *et al.* (2002); Nadler *et al.* (2004)
Endophenotypes	Increased sensitivity to psychostimulants (e.g. amphetamine and cocaine)	Measurement of locomotor activation following administration of psychostimulants	van den Buuse *et al.* (2005)
	Impaired sensorimotor gating (pre-attention)	PPI of startle response	Geyer *et al.* (2001)
	Impaired auditory evoked potentials	Auditory-evoked potential measurement	Connolly *et al.* (2003)
	Impaired LI	Shuttle-box, fear-conditioning	Feldon and Weiner (1991); Mongeau *et al.* (2007)
	Impaired mismatch negativity	Mismatch negativity in anesthetized rodents	Umbricht *et al.* (2005)
	Alterations in neurochemistry	Neurochemistry and microdialysis measurements	Di Matteo *et al.* (2008); Lodge and Grace (2008)
	Sleep disturbances	Electroencephalogram measurements, sleep-wake cycles	Cohrs (2008); Dzirasa *et al.* (2006);
	Mood (anxiety)	Open field, EPM, light/dark, holeboard, marble burying; stress-induced hyperthermia	Borsini *et al.* (1989); Crawley (1981); Gardner and Piper (1982); Njung'e and Handley (1991); Prut and Belzung (2003); Rodgers and Johnson (1995);
	Mood (depression)	Forced swim test, tail suspension test, learned helplessness	Porsolt *et al.* (1977); Seligman and Beagley (1975); Steru *et al.* (1985)

Human correlate	Animal model	References
Self-care	Grooming, body weight, coat condition, general health, barbering, etc.	Audet *et al.* (2006)

Table 2

Literature summary of the effects of exposure to DVD deficiency in rodents

Species	Strain	Sex	Deficiency	Exposure timing	Age at testing	Outcome (increase (↑) or decrease (↓) relative to control diet)	References
Rat	Sprague-Dawley	F and M	Vitamin D (0 IU/kg; Dyets, Inc, Bethlehem PA, USA)	DVD	PND0	↑ Lateral ventricles ↓ Cortical thickness ↑ Mitotic cells in DG, Hypo, BG ↓ NGF and GDNF ↓ $p75^{NTR}$ mRNA and protein expression	Eyles *et al.* (2003)
Rat	Sprague-Dawley	F and M*	Vitamin D (0 IU/kg with 2mM Ca; Dyets, Inc, Bethlehem PA, USA)	DVD vs. weaning (DVD-PND21) vs. Life (DVD-PND70)	PND70	↑ Locomotion in holeboard test and EPM in DVD group only	Burne *et al.* (2004a)
Rat	Sprague-Dawley	F and M*	Vitamin D (0 IU/kg; Dyets, Inc, Bethlehem PA, USA)	DVD vs. weaning (DVD-PND21) vs. Life (DVD-PND70) vs. AVD (PND 35–70)	PND35 and PND70	↓ PPI in Life group only at PND 70	Burne *et al.* (2004b)
Rat	Sprague-Dawley		Vitamin D (0 IU/kg; Dyets, Inc, Bethlehem PA, USA)	DVD	ED19, ED21, PND0, P7	↓ Apoptotic cells in BG, Hypo, cingulate, DG at E21 and E23 ↑ Mitotic cells in dentate at E19 and E21 and BG at P7 ↓ Pro-apoptotic gene expression ↑ Cell cycle progression (pro-mitotic) gene expression	Ko *et al.* (2004)
Rat	Sprague-Dawley	M	Vitamin D (0 IU/kg with 2mM Ca; ssniff Spezialdiäten GmbH, Soest, Germany)	DVD	PND56	Impaired LI (in an active avoidance task) ↓ Habituation over time in holeboard ↓ Exploratory behavior of novel olfactory stimuli (Day 5 of holeboard) ↑ Learning skill on brightness discrimination Y-chamber	Becker *et al.* (2005)

Species	Strain	Sex	Deficiency	Exposure timing	Age at testing	Outcome (increase (↑) or decrease (↓) relative to control diet)	References
Rat	Sprague-Dawley	F and M†	Vitamin D (0 IU/kg; Dyets, Inc, Bethlehem PA, USA)	DVD vs. weaning (DVD-PND21)	PND70	↑ Lateral ventricles in weaning group ↓ Anterior commissure in DVD group ↓ NGF in both groups ↓ GABA-$A_{\alpha 4}$ and MAP-2 gene expression in both groups ↓ NF-L gene expression in DVD group	Feron *et al.* (2005)
Rat	Sprague-Dawley	M	Vitamin D (0 IU/kg; Dyets, Inc, Bethlehem PA, USA)	DVD	PND70	↑ Locomotion in holeboard test ↑ MK-801-induced locomotion (prevented with acute haloperidol) ↑ Locomotion in open field (prevented with acute haloperidol)	Kesby *et al.* (2006)
Rat	Sprague-Dawley	M	Vitamin D (0 IU/kg; Dyets, Inc, Bethlehem PA, USA)	DVD	PND70	↑ Locomotion in open field	Eyles *et al.* (2006)
Rat	Sprague-Dawley	M	Vitamin D (0 IU/kg with 2 mM Ca; ssniff Spezialdiäten GmbH, Soest, Germany)	DVD	PND56	↓ Head dipping (prevented with subchronic haloperidol and CHPG) ↓ Habituation in holeboard test (normalized with subchronic haloperidol, CHPG and risperidone)	Becker and Grecksch (2006)
Rat	Sprague-Dawley	F and M*	Vitamin D (0 IU/kg; Dyets, Inc, Bethlehem PA, USA)	DVD	PND56	↑ Locomotion in the open field (prevented with 5-min acute restraint stress before open field)	Burne *et al.* (2006)
Rat	Sprague-Dawley	F and M	Vitamin D (0 IU/kg; Dyets, Inc, Bethlehem PA, USA)	DVD	PND70	Dysreguiated expression of 17 proteins in the FC Dysregulated expression of 23 proteins in the Hipp Dysregulated expression of Hs7C, Tbb1, EnoG and ATPb proteins in both FC and Hipp	Almeras *et al.* (2007)
Rat	Sprague-Dawley	F and M	Vitamin D (0 IU/kg; Dyets, Inc, Bethlehem PA, USA)	DVD	PND0	↑ Number of neurosphere in SVZ cultures	Cui *et al.* (2007)

Species	Strain	Sex	Deficiency	Exposure timing	Age at testing	Outcome (increase (↑) or decrease (↓) relative to control diet)	References
Rat	Sprague-Dawley	F and M	Vitamin D (0 IU/kg; Dyets, Inc, Bethlehem PA, USA)	DVD	PND70	Dysregulated expression of 74 genes	Eyles *et al.* (2007)
Rat	Sprague-Dawley	M	Vitamin D (0 IU/kg; Dyets, Inc, Bethlehem PA, USA)	Early DVD (4 weeks before mating) vs. late DVD (E0–E21) vs. full DVD	PND70	↑ MK-801-induced locomotion in late and full DVD	O'Loan *et al.* (2007)
Rat	Sprague-Dawley	M	Vitamin D (0 IU/kg; Dyets, Inc, Bethlehem PA, USA)	DVD	PND70	↓ Protein expression of 22 proteins in NAc ↑ Protein expression of 13 proteins in NAc	McGrath *et al.* (2008)
Rat	Sprague-Dawley	M	Vitamin D (0 IU/kg; Dyets, Inc, Bethlehem PA, USA)	DVD	P0	↑ DOPAC/HVA in forebrain ↓ HVA/DA in forebrain ↓ COMT expression	Kesby *et al.* (2009)
Rat	Sprague-Dawley	F and M†	Vitamin D (0 IU/kg; Dyets, Inc, Bethlehem PA, USA)	DVD	ED12 and ED15	↓ Nurr1 expression at ED12 and ED15 ↓ p57Kip2 expression at ED15 (Fetal mesencephalon)	Cui *et al.* (2010)
Rat	Sprague-Dawley	F and M	Vitamin D (0 IU/kg; Dyets, Inc, Bethlehem PA, USA)	DVD	PND35 and PND70	↑ Amphetamine-induced locomotion ↑ DAT density in CPu ↑ DAT affinity in the Acb (females only, PND 70)	Kesby *et al.* (2010)
Rat	Sprague-Dawley	F	Vitamin D (0 IU/kg; Dyets, Inc, Bethlehem PA, USA)	DVD	PND0 and Tested Dams	↑ Pup retrieval time ↑ Pup-directed activities (sniffing and carrying) ↓ Latency for self-grooming	Burne *et al.* (2011)
Rat	Sprague-Dawley	F and M	Vitamin D (0 IU/kg; Dyets, Inc, Bethlehem PA, USA)	DVD	PND150-180	↑ MK-801-induced locomotion ↑ Mk-801-induced acoustic startle ↓ MK-801 binding in the CPu	Kesby *et al.* (2012)
Rat	Sprague-Dawley	F and M*	Vitamin D (0 IU/kg; Dyets, Inc, Bethlehem PA, USA)	DVD	PND140	↑ Premature responses (reversed with acute clozapine) ↑ Lack responses in non-target trials (Trials 1–14) (reversed with acute clozapine) ↓ Reward latency	Turner *et al.* (2013)
Rat	Sprague-Dawley	F and M*	Vitamin D (0 IU/kg; Specialty Feeds, Glen Forrest,	DVD	PND180	↑ THC-induced PPI	Burne *et al.* (2014)

Species	Strain	Sex	Deficiency	Exposure timing	Age at testing	Outcome (increase (↑) or decrease (↓) relative to control diet)	References
			Western Australia)				
Rat	Sprague-Dawley	F and M	Vitamin D (0, 1.5, 3.3, 6, and 10 IU/g; Purina Mills, LLC, TestDiet, St. Louis MO, USA)	Mating till weaning (PND18)	PND35-40 and PND100-105	↑ Grooming behavior in EPM at PND35-40 in 0 group	Pan *et al.* (2014)
Rat	Sprague-Dawley	F and M*	Vitamin D (0 IU/kg; Specialty Feeds, Glen Forrest, Western Australia)	DVD	PND210-290	↓ Training sessions required to meet criteria in the rodent gambling task ↑ Food rewards per session (overall increased performance)	Peak *et al.* (2015)
Mice	129/SvJ (129) and C57BL/6J	F and M*	Vitamin D (0 IU/kg; Dyets, Inc, Bethlehem PA, USA)	DVD	PND70	↑ Head dipping in both strains ↓ Habituation to holeboard test in B6J ↑ Locomotion in open field and holeboard in 129	Harms *et al.* (2008)
Mice	C57BL/6J	M	Vitamin D (0 IU/kg; INRA, France)	DVD	PND210 and PND420	↓ Lateral ventricles PND210 ↓ Learning in olfactory tubing maze (Hipp-dependent memory task)	Fernandes de Abreu *et al.* (2010)
Mice	C57BL/6J (B6J) and 129/X1SvJ	F and M	Vitamin D (0 IU/kg; Dyets, Inc, Bethlehem PA, USA)	DVD	PND0 (MRI) and PND70 (MRI and behavior)	↓ Hipp in B6J females at PND0 ↓ Lateral ventricles in B6J males at PND70 ↑ Striatum in B6J males at PND70	Harms *et al.* (2012a)
Mice	C57BL/6J	F and M	Vitamin D (0 IU/kg; Specialty Feeds, Glen Forrest, Western Australia)	DVD	PND140	↑ Repetitive responses (nose poke) to target stimuli in 5C-CPT	Harms *et al.* (2012b)
Mice	BALB/c	F and M	Vitamin D (0 IU/kg with 25 g/kg Ca and 15.3 MJ/kg; Specialty Feeds, Glen Forrest, Western Australia)	DVD	ED14.5 and ED17.5	↓ Crown-rump length at ED17.5 ↓ Lambda-bregma length at ED17.5 ↓ Lateral ventricle volume at ED17.5 ↓ *Bdnf* gene expression at ED14.5 ↑ *Bdnf* gene expression at ED175 ↑ *Tgf-ß1* gene expression at ED17.5	Hawes *et al.* (2015)

Species	Strain	Sex	Deficiency	Exposure timing	Age at testing	Outcome (increase (↑) or decrease (↓) relative to control diet)	References
						↓ *Foxp2* gene expression at ED14.5 ↑ *Foxp2* gene expression at ED17.5 ↓ *Th* gene expression at ED175 in F ↓ Foxp2 expression in cortex at ED17.5 in F ↓ TH expression in SN at ED175 in F	
Mice	BALB/c	F and M	Vitamin D (0 IU/kg with 25 g/kg Ca and 15.3 MJ/kg; Specialty Feeds, Glen Forrest, Western Australia)	DVD	ED14.5 and ED17.5	↑ Maternal CORT levels ↑ Fetal glucocorticoid exposure ↓ Placental vascular development	Tesic *et al.* (2015)

Acb, accumbens; AVD, adult vitamin D deficiency; BG, basal ganglia; Ca, calcium; Cingulate, cingulate gyrus of the cortex; COMT catechol-*O*-methyl transferase; CORT, corticosterone; CPu, caudate putamen; DG, dentate gyrus of the hippocampus; DOPAC, 3,4-dihydroxyphenylacetic acid; ED, embryonic day; F, female; FC, frontal cortex; Foxp2, forkhead box protein P2; GDNF, glial cell line-derived neurotrophic factor; Hipp, hippocampus; HVA, homovanillic acid; Hypo, hypothalamus; M, male; NAc, nucleus accumbens; PND, postnatal day; SN, substantia nigra; SVZ, subventricular zone.

*Female and male offspring were tested; however, data were pooled for analysis because of no significant effect of vitamin D diet × sex effects.

†Tissues from female and males were taken and data pooled without analyzing separately.

Table 3

Comparison of findings of DVD deficiency in rats vs. mice. ND = No Difference Observed

Behavior	Sprague-Dawley rat	Inbred mice	References
PPI	ND	ND	Burne *et al.* (2014); Harms *et al.* (2008); Kesby *et al.* (2006, 2012)
Attentional processing: 5C-SRT	ND	ND	Harms *et al.* (2012b); Turner *et al.* (2013)
Sustained attentional processing: response inhibition in 5C-CPT	↓	↓	Harms *et al.* (2012b); Turner *et al.* (2013)
LI	Disrupted	ND	Becker *et al.* (2005); Harms *et al.* (2012b)
Head dipping: holeboard test	↓	↑	Becker and Grecksch (2006); Becker *et al.* (2005); Harms *et al.* (2008)
Habituation: holeboard test	↓	↓ in B6J ND in 129	Becker and Grecksch (2006); Becker *et al.* (2005); Harms *et al.* (2008)
Social interaction	ND	ND	Burne *et al.* (2004a); Harms *et al.* (2008)
Anxiety-like behavior: EPM	ND	ND	Burne *et al.* (2004a); Harms *et al.* (2008)
Spontaneous hyperlocomotion	↑	↑ in 129 ND in B6J	Burne *et al.* (2004a, 2006); Eyles *et al.* (2006); Harms *et al.* (2008); Kesby *et al.* (2006)
MK-801-induced locomotion	↑	ND	Harms *et al.* (2012a); Kesby *et al.* (2006, 2012); O'Loan *et al.* (2007)
Amphetamine-induced locomotion	↑	ND	Harms *et al.* (2012a); Kesby *et al.* (2010)
Lateral ventricle size	↑	↓	Eyles *et al.* (2003); Fernandes de Abreu *et al.* (2010); Feron *et al.* (2005); Harms *et al.* (2012a); Hawes *et al.* (2015)