Psychiatry Research: Neuroimaging ∎ (∎∎∎∎) ∎∎∎–∎∎∎

Contents lists available at ScienceDirect

Psychiatry Research: Neuroimaging

journal homepage: www.elsevier.com/locate/psychresns

Serum vitamin D and hippocampal gray matter volume in schizophrenia

Venkataram Shivakumar [a,b,c], Sunil V. Kalmady [a,b], Anekal C. Amaresha [a,b], Dania Jose [a,b], Janardhanan C. Narayanaswamy [a,b], Sri Mahavir Agarwal [a,b], Boban Joseph [a,b], Ganesan Venkatasubramanian [a,b,*], Vasanthapuram Ravi [d], Matcheri S. Keshavan [e], Bangalore N. Gangadhar [a]

[a] Schizophrenia Clinic, Department of Psychiatry, NIMHANS, Bangalore, India
[b] Translational Psychiatry Laboratory, Neurobiology Research Centre, NIMHANS, Bangalore, India
[c] Department of Clinical Neurosciences, NIMHANS, Bangalore, India
[d] Department of Neurovirology, NIMHANS, Bangalore, India
[e] Department of Psychiatry, Beth Israel Deaconess Medical Center and Massachusetts Mental Health Center, Harvard Medical School, Boston, MA, USA

ARTICLE INFO

Article history:
Received 1 May 2015
Accepted 21 June 2015

Keywords:
Schizophrenia
Vitamin D
Hippocampus

ABSTRACT

Disparate lines of evidence including epidemiological and case-control studies have increasingly implicated vitamin D in the pathogenesis of schizophrenia. Vitamin D deficiency can lead to dysfunction of the hippocampus – a brain region hypothesized to be critically involved in schizophrenia. In this study, we examined for potential association between serum vitamin D level and hippocampal gray matter volume in antipsychotic-naïve or antipsychotic-free schizophrenia patients ($n=35$). Serum vitamin D level was estimated using 25-OH vitamin D immunoassay. Optimized voxel-based morphometry was used to analyze 3-Tesla magnetic resonance imaging (MRI) (1-mm slice thickness). Ninety-seven percent of the schizophrenia patients ($n=34$) had sub-optimal levels of serum vitamin D (83%, deficiency; 14%, insufficiency). A significant positive correlation was seen between vitamin D and regional gray matter volume in the right hippocampus after controlling for age, years of education and total intracranial volume (Montreal Neurological Institute (MNI) coordinates: $x=35$, $y=-18$, $z=-8$; $t=4.34$ $pFWE_{Corrected}=0.018$). These observations support a potential role of vitamin D deficiency in mediating hippocampal volume deficits, possibly through neurotrophic, neuroimmunomodulatory and glutamatergic effects.

1. Introduction

Disparate lines of evidence have implicated vitamin D in the pathogenesis of schizophrenia. Infant cohort studies have revealed elevated risk for schizophrenia in infants with deficient vitamin D (McGrath et al., 2010) and reduced risk in those who had received supplementation (McGrath et al., 2004). Deficient serum levels of vitamin D have been observed in patients with first episode psychosis (Graham et al., 2014) as well as in patients with chronic schizophrenia (Humble et al., 2010). A recent meta-analysis on the relationship between vitamin D and psychosis reported a moderately significant reduction in serum levels of vitamin D in schizophrenia patients compared with healthy controls and a trend for lower levels compared with other psychoses (Belvederi Murri et al., 2013).

Following the discovery of vitamin D receptors (VDRs) in neurons and glial cells (Garcion et al., 2002), studies have increasingly demonstrated the importance of vitamin D in early brain development as well as in facilitating optimal brain function (Eyles et al., 2003). Vitamin D can cross the blood–brain barrier and stimulate a broad range of functions by binding to VDRs (Kalueff et al., 2006). The action of vitamin D in the brain is largely considered to be neuroprotective (Garcion et al., 2002). It is reported to be involved in the biosynthesis of neurotransmitters and neurotrophic factors like brain-derived neurotrophic factor (BDNF) (Kiraly et al., 2006). It is also implicated in the reduction of free radicals and reactive oxygen species, and hence confers neuroprotection (Garcion et al., 1997; Wang et al., 2001). Since deficient BDNF (Kalmady et al., 2013) and increased oxidative stress (Wu et al., 2013) have been associated with schizophrenia, these effects mediated by vitamin D through VDRs could be critical in this

* Corresponding author at: Department of Psychiatry, National Institute of Mental Health and Neurosciences (NIMHANS), Bangalore 560029, India.
E-mail address: venkat.nimhans@yahoo.com (G. Venkatasubramanian).

http://dx.doi.org/10.1016/j.pscychresns.2015.06.006
0925-4927/

disorder.

Interestingly, both deficient BDNF (Erickson et al., 2010) and as excessive oxidative stress (Wang and Michaelis, 2010) can result in abnormalities of the hippocampus – a brain region that hypothetically plays a critical role in schizophrenia pathogenesis (Heckers and Konradi, 2010). Hippocampal abnormalities in schizophrenia manifest in the form of smaller hippocampal volume, altered number of neurons, reduced functional activity and abnormal functioning of genes expressed by the hippocampus (Harrison, 2004; Heckers and Konradi, 2010). Among these, smaller hippocampal volume in schizophrenia is a well-replicated finding in many studies (Steen et al., 2006; Heckers and Konradi, 2010). More importantly, the hippocampus is one of the brain regions with maximal concentrations of VDRs (Eyles et al., 2005); vitamin D has been shown to play a critical role in hippocampal cell survival through its neuroprotective effects (Langub et al., 2001).

All of these observations suggest that vitamin D deficiency in schizophrenia might be associated with hippocampal abnormalities. To date, no study has looked into the association between serum vitamin D and hippocampal volume in schizophrenia. In this study therefore, we examined the association between serum vitamin D level and hippocampal gray matter (GM) volume in antipsychotic-naïve or anti-sychotic-free schizophrenia patients. We hypothesized that hippocampal GM volume would positively correlate with serum vitamin D levels in schizophrenia patients.

2. Methods

2.1. Clinical profile

Schizophrenia patients ($n=35$; mean age$=32.14\pm6.6$; mean years of education$=9.91\pm4.23$; 20 men) attending the clinical services of the National Institute of Mental Health and Neurosciences (India) participated in the study. They were either antipsychotic-naïve ($n=25$, i.e., never treated with any psychotropic medications including antipsychotics) or antipsychotic-free ($n=10$, not having been treated with oral medication for at least 6 weeks or with depot antipsychotics for 3 months). Diagnosis of schizophrenia (DSM-IV-TR) was established using the Mini International Neuropsychiatric Interview Plus (Sheehan et al., 1998) and was confirmed independently by two psychiatrists with a comprehensive clinical interview. The details related to onset of illness and antipsychotic-naïve or antipsychotic-free status were ascertained by reliable information obtained from at least one first degree relative. Clinical symptoms were assessed using the Scale for the Assessment of Positive Symptoms (SAPS) (Andreasen, 1984) and the Scale for the Assessment of Negative Symptoms (SANS) (Andreasen, 1983). None of the patients had clinical features suggestive of substance abuse or dependence. None had co-morbid medical or neurological diagnoses. All the subjects were right-handed (established using the Edinburgh Handedness Inventory). After complete description of the study to the subjects, written informed consent was obtained. The Institute's ethics committee approved the study.

2.2. Serum vitamin-D assay

Blood samples were collected from all subjects between 08:00 and 09:00 hours (A.M) after a 12-h overnight fast. Blood was drawn from an antecubital vein into a serum separator tube (SST™ II Advance, BD Vacutainer® tubes, Becton & Dickinson, NJ, USA), mixed well by inversion and allowed to clot for 30 min before centrifugation for 15 min at 1000*g*. Serum was separated, aliquoted and stored at −80 °C. Vitamin D levels were determined using a high sensitivity quantitative competitive enzyme immunoassay kit (DLD-diagnostika GMBH, Hamburg, Germany). This ELISA kit was equally specific for both vitamin D2 (ergocalciferol) and D3 (cholecalciferol), and hence determined the concentration of both. The dynamic range of the assay was 0–120 ng/ml and sensitivity was 1.9 ng/ml. Samples were run in duplicate and the average coefficient of variation was less than 15%.

2.3. Brain imaging: acquisition and processing

T_1-weighted structural magnetic resonance imaging (MRI) of the brain was acquired using the following parameters, repetition time$=8.1$ ms, echo time$=3.7$ ms, nutation angle$=8°$, field of view$=256$ mm, slice thickness$=1$ mm without inter-slice gap, number of excitations$=1$, matrix$=256\times256$ (3 T, Siemens Skyra Scanner). Voxel-based morphometry (VBM) analysis was performed using SPM8 (http://www.fil.ion.ucl.ac.uk/spm) implemented within MATLAB (R2013a, Math-Works, Natick, MA, USA). MR images were initially segmented into gray matter (GM), white matter (WM) and cerebrospinal fluid (CSF) using the standard unified segmentation model in SPM8 (Ashburner and Friston, 2005). GM population templates were then generated from the entire image dataset using the diffeomorphic anatomical registration with the exponentiated Lie algebra (DARTEL) technique (Ashburner, 2007). Then, after an initial affine registration of the GM DARTEL templates to the tissue probability maps in Montreal Neurological Institute (MNI) space (http://www.mni.mcgill.ca/), non-linear warping of GM images was performed to the DARTEL GM template in MNI space. Next, images were modulated to ensure that relative volumes of GM were preserved following the spatial normalization procedure. Lastly, images were smoothed with an 8-mm full width at half-maximum Gaussian kernel. After spatial pre-processing, the normalized, modulated, and smoothed, GM images were used for statistical analysis.

2.4. Image analysis

The hypothesis that serum vitamin D positively correlates with GM volume in the hippocampus was tested in SPM8 with age, years of education and total intracranial volume as covariates of no interest. The region of interest (ROI) method was applied. A standard hippocampus mask was defined using the Automated Anatomical Labeling (Tzourio-Mazoyer et al., 2002) system with the Wake Forest University (WFU) Pick-Atlas tool (Maldjian et al., 2003). To avoid possible edge effects between different tissue types, all voxels with GM values of less than 0.1 (absolute threshold masking) were excluded. To correct for multiple comparisons within the hippocampus mask, a Small Volume Correction (SVC) was applied (threshold for significance: $p<0.05$ using family-wise error (FWE) correction).

3. Results

The Serum vitamin D (mean ± SD) level determined in the study subjects was 14.5 ± 5.7 ng/ml, with 29 patients having deficient levels (<20 ng/ml) and 5 insufficient levels (20–29 ng/ml) relative to control norms (Harinarayan et al., 2008; Holick et al., 2011). The mean ± SD clinical symptom scores were as follows: SAPS total$=25.26\pm29.87$; SANS total$=24.5\pm13.05$. Mean ± SD illness duration of the sample was 37.11 ± 35.73 months (median$=33$).

A significant positive correlation was seen between serum vitamin D level and GM volume in the right hippocampus (MNI coordinates of peak significance: $x=35$, $y=-18$, $z=-8$; $T=4.34$, $p_{SVC\text{-}FWE}=0.018$). To illustrate further the significant positive

Please cite this article as: Shivakumar, V., et al., Serum vitamin D and hippocampal gray matter volume in schizophrenia. Psychiatry Research: Neuroimaging (2015), http://dx.doi.org/10.1016/j.pscychresns.2015.06.006

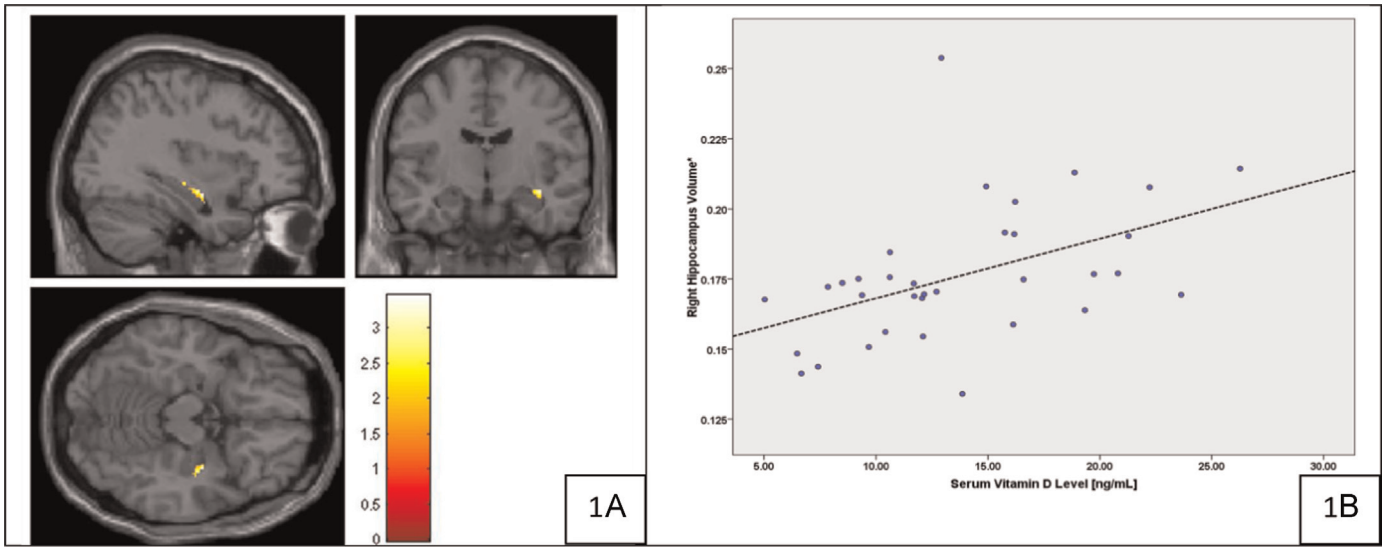

Fig. 1. Lower levels of serum vitamin D levels were associated with decreased grey matter volume in the right hippocampus in schizophrenia patients ($N=35$). (1A) Significant positive correlation between serum vitamin D and right hippocampus volume in schizophrenia patients. For display purpose the images are thresholded at uncorrected $p=0.05$. (1B) Scatter Plot depicting significant positive correlation between serum vitamin D level and right hippocampus volume. *Average gray matter volume [mean signal intensity values] in the extracted cluster of significance ($x=35$, $y=-18$, $z=-8$).

correlation, the GM image volume/density at the voxel coordinates localizing the peak correlation with serum vitamin D was extracted using MARSBAR (Brett et al., 2002). Plotting these values against serum vitamin D levels ascertained the significance ($r=0.51$, $p=0.002$) (Fig. 1).

Right hippocampal volume correlated negatively with the SAPS total score at an uncorrected threshold of $p_{uncorr}=0.016$, but this did not survive the correction for multiple comparisons. There was no significant relationship between vitamin D and left hippocampal volume. Serum vitamin D did not correlate significantly with symptom scores.

4. Discussion

In this study, 97% of antipsychotic-naïve or antipsychotic-free schizophrenia patients had sub-optimal (83%, deficiency; 14%, insufficiency) levels of serum vitamin D. The serum levels of vitamin D observed in our patients (14.5 ± 5.7 ng/ml) add to the existing evidence of vitamin D deficiency in schizophrenia (Graham et al., 2014; Itzhaky et al., 2012). A novel observation in our study was the significant positive correlation between serum vitamin D level and right hippocampal GM volume. We propose that this relationship might be mediated by neurotrophic, neuroimmunomodulatory and glutamatergic effects of vitamin D as elaborated further.

Several studies have demonstrated a decrease in the concentrations of neurotrophins in schizophrenia patients and their association with psychopathology (Buckley et al., 2007; Kalmady et al., 2013). Further, low levels of neurotrophins such as BDNF have been associated with reduction in hippocampal volume in schizophrenia (Erickson et al., 2010). Vitamin D is known to upregulate many of these neurotrophins by increasing the gene expression (Wion et al., 1991; Naveilhan et al., 1996a, 1996b). In addition, animal studies have also demonstrated the ability of vitamin D to retard the degradation of the hippocampus, conferring general neuroprotection (Landfield and Cadwallader-Neal, 1998). Besides this, vitamin D can also confer neuroprotection to the hippocampus and other brain structures by inducing glial cell line-derived neurotrophic factor (GDNF) and hence reducing the oxidative damage caused by reactive oxygen species (Wang et al., 2001).

Another probable mechanism, by which vitamin D confers neuroprotection indirectly, is through its immune-modulating properties. Vitamin D is known to modulate inflammation by decreasing the production of pro-inflammatory cytokines and increasing the production of anti-inflammatory cytokines (McCann and Ames, 2008). In particular, interleukin-6 (IL-6), which is high in schizophrenia patients (Miller et al., 2011), also has a negative association with hippocampal volume (Kalmady et al., 2014). Hypovitaminosis D might enhance the IL-6 mediated damage to the hippocampus (Samuelsson et al., 2006), thereby resulting in volume loss.

Very recently, proline elevation due to reduced proline dehydrogenase gene (*PRODH*) expression with resultant dysregulation of neurotransmission has been reported as the mechanistic basis for the link between vitamin D insufficiency and schizophrenia risk (Clelland et al., 2014), since vitamin D has been shown to significantly up-regulate *PRODH* gene expression. *PRODH* facilitates conversion of proline to glutamate (Phang et al., 2010). Moreover, *PRODH* is located within chromosome 22q11-a region of common microdeletion that confers the highest genetic risk for schizophrenia apart from that shared by monozygotic twins (Karayiorgou and Gogos, 2004). Genetic aberrations involving *PRODH* with resultant hyperprolinemia have been linked with schizophrenia risk (Willis et al., 2008). Also, proline has a neuromodulatory function in glutamatergic synapses in the hippocampus (Cohen and Nadler, 1997); hence, hyperprolinemia might contribute to glutamate abnormalities in schizophrenia. The transcription factor SOX2 which is critical for *PRODH* function is preferentially expressed in the hippocampus (Suntsova et al., 2013). Interestingly, glutamate abnormalities of the hippocampus have been demonstrated in schizophrenia patients with 22q11 deletion. Contextually, it is important to note that the hippocampus is one the brain regions with maximum concentration of VDRs (Eyles et al., 2005). Hence, it is possible that the neural effects of vitamin D mediated through *PRODH* might underlie the hippocampal volume deficit in schizophrenia.

Although assessment of schizophrenia patients with minimal confounds of antipsychotic treatment effects/illness chronicity adds to the methodological rigor of this study, the results have to be interpreted in the context of the following potential limitations.

Please cite this article as: Shivakumar, V., et al., Serum vitamin D and hippocampal gray matter volume in schizophrenia. Psychiatry Research: Neuroimaging (2015), http://dx.doi.org/10.1016/j.pscychresns.2015.06.006

The causal factors of low vitamin D noted across studies, such as seasonality of sampling (Andersen et al., 2013), dietary practices, nature of work and sun exposure (Mithal et al., 2009), were not taken into consideration in this study. Body-mass index is also reported to have a significant effect on serum vitamin D levels (Rey-Sanchez et al., 2009), which has not been evaluated in the current study. However, none of these factors have reportedly explained the low vitamin D status in patients with respect to controls (Belvederi Murri et al., 2013). Moreover, it has to be acknowledged that the correlational association between serum vitamin D and right hippocampal volume does not necessarily indicate a causative mechanism; nonetheless, it suggests that vitamin D could have a role in the pathogenesis of schizophrenia.

In summary, our study findings add to the increasing literature of high prevalence of hypovitaminosis D in schizophrenia patients. Moreover, we observed that the lower the level of serum vitamin D, the smaller was the right hippocampal GM volume in these patients. Further studies are required to replicate this finding; moreover, the mechanistic link between serum vitamin D and brain abnormalities needs further elucidation with concurrent assessment of neurotrophic factors like BDNF, cytokines like IL-6, proline level and *PRODH* expression.

Acknowledgments

This work is supported by the CEIB Programme Support Grant to G.V. (BT/PR5322/COE/34/8/2012). V.S. & B.J. are supported by Department of Biotechnology, Government of India. S.V.K., A.C.A. & S.M.A. are supported by the Wellcome Trust/DBT India Alliance. J.C. N. is supported by the INSPIRE faculty; award by the Department of Science and Technology, Government of India. D.J. is supported by the Department of Science and Technology, Government of India.

References

Andersen, R., Brot, C., Jakobsen, J., Mejborn, H., Molgaard, C., Skovgaard, L.T., Trolle, E., Tetens, I., Ovesen, L., 2013. Seasonal changes in vitamin D status among Danish adolescent girls and elderly women: the influence of sun exposure and vitamin D intake. Eur. J. Clin. Nutr. 67, 270–274.

Andreasen, N., 1983. The Scale for the Assessment of Negative Symptoms. University of Iowa, Iowa City.

Andreasen, N., 1984. The Scale for the Assessment of Positive Symptoms. University of Iowa, Iowa City.

Ashburner, J., 2007. A fast diffeomorphic image registration algorithm. Neuroimage 38, 95–113.

Ashburner, J., Friston, K.J., 2005. Unified segmentation. Neuroimage 26, 839–851.

Belvederi Murri, M., Respino, M., Masotti, M., Innamorati, M., Mondelli, V., Pariante, C., Amore, M., 2013. Vitamin D and psychosis: mini meta-analysis. Schizophr. Res. 150, 235–239.

Brett, M., Anton, J.-L., Valabregue, R., Poline, J.-B., 2002. Region of interest analysis using an SPM toolbox. Presented at the 8th International Conference on Functional Mapping of the Human Brain. NeuroImage, pp. 16.

Buckley, P.F., Mahadik, S., Pillai, A., Terry Jr., A., 2007. Neurotrophins and schizophrenia. Schizophr. Res. 94, 1–11.

Clelland, J.D., Read, L.L., Drouet, V., Kaon, A., Kelly, A., Duff, K.E., Nadrich, R.H., Rajparia, A., Clelland, C.L., 2014. Vitamin D insufficiency and schizophrenia risk: evaluation of hyperprolinemia as a mediator of association. Schizophrenia Research 156 (1), 15–22.

Cohen, S.M., Nadler, J.V., 1997. Proline-induced inhibition of glutamate release in hippocampal area CA1. Brain Res. 769, 333–339.

Erickson, K.I., Prakash, R.S., Voss, M.W., Chaddock, L., Heo, S., McLaren, M., Pence, B. D., Martin, S.A., Vieira, V.J., Woods, J.A., McAuley, E., Kramer, A.F., 2010. Brain-derived neurotrophic factor is associated with age-related decline in hippocampal volume. J. Neurosci. 30, 5368–5375.

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

Eyles, D.W., Smith, S., Kinobe, R., Hewison, M., McGrath, J.J., 2005. Distribution of the vitamin D receptor and 1 alpha-hydroxylase in human brain. J. Chem. Neuroanat. 29, 21–30.

Garcion, E., Nataf, S., Berod, A., Darcy, F., Brachet, P., 1997. 1,25-Dihydroxyvitamin D3 inhibits the expression of inducible nitric oxide synthase in rat central nervous system during experimental allergic encephalomyelitis. Mol. Brain Res. 45, 255–267.

Garcion, E., Wion-Barbot, N., Montero-Menei, C.N., Berger, F., Wion, D., 2002. New clues about vitamin D functions in the nervous system. Trends Endocrinol. Metab. 13, 100–105.

Graham, K.A., Keefe, R.S., Lieberman, J.A., Calikoglu, A.S., Lansing, K.M., Perkins, D.O., 2014. Relationship of low vitamin D status with positive, negative and cognitive symptom domains in people with first-episode schizophrenia. Early Interv. Psychiatry, http://dx.doi.org/10.1111/eip.12122 (online).

Harinarayan, C.V., Ramalakshmi, T., Prasad, U.V., Sudhakar, D., 2008. Vitamin D status in Andhra Pradesh: a population based study. Indian J. Med. Res. 127, 211–218.

Harrison, P.J., 2004. The hippocampus in schizophrenia: a review of the neuropathological evidence and its pathophysiological implications. Psychopharmacology 174, 151–162.

Heckers, S., Konradi, C., 2010. Hippocampal pathology in schizophrenia. Curr. Top. Behav. Eurosci. 4, 529–553.

Holick, M.F., Binkley, N.C., Bischoff-Ferrari, H.A., Gordon, C.M., Hanley, D.A., Heaney, R.P., Murad, M.H., Weaver, C.M., 2011. Evaluation, treatment, and prevention of vitamin D deficiency: an endocrine society clinical practice guideline. J. Clin. Endocrinol. Metab. 96, 1911–1930.

Humble, M.B., Gustafsson, S., Bejerot, S., 2010. Low serum levels of 25-hydroxyvitamin D (25-OHD) among psychiatric out-patients in Sweden: relations with season, age, ethnic origin and psychiatric diagnosis. J. Steroid Biochem. Mol. Biol. 121, 467–470.

Itzhaky, D., Amital, D., Gorden, K., Bogomolni, A., Arnson, Y., Amital, H., 2012. Low serum vitamin D concentrations in patients with schizophrenia. Israel Med. Assoc. J. 14, 88–92.

Kalmady, S.V., Venkatasubramanian, G., Shivakumar, V., Gautham, S., Subramaniam, A., Jose, D.A., Maitra, A., Ravi, V., Gangadhar, B.N., 2014. Relationship between Interleukin-6 gene polymorphism and hippocampal volume in antipsychotic-naive schizophrenia: evidence for differential susceptibility? PLoS One 9, e96021.

Kalmady, S.V., Venkatasubramanian, G., Shivakumar, V., Jose, D., Ravi, V., Gangadhar, B.N., 2013. Relationship between brain-derived neurotrophic factor and Schneiderian first rank symptoms in antipsychotic-naive schizophrenia. Front. Psychiatry 4, 64.

Kalueff, A.V., Minasyan, A., Keisala, T., Kuuslahti, M., Miettinen, S., Tuohimaa, P., 2006. The vitamin D neuroendocrine system as a target for novel neurotropic drugs. CNS Neurol. Disord. Drug Targets 5, 363–371.

Karayiorgou, M., Gogos, J.A., 2004. The molecular genetics of the 22q11-associated schizophrenia. Mol. Brain Res. 132, 95–104.

Kiraly, S.J., Kiraly, M.A., Hawe, R.D., Makhani, N., 2006. Vitamin D as a neuroactive substance: review. Sci. World J. 6, 125–139.

Landfield, P.W., Cadwallader-Neal, L., 1998. Long-term treatment with calcitriol (1,25(OH)2 vit D3) retards a biomarker of hippocampal aging in rats. Neurobiol. Aging 19, 469–477.

Langub, M.C., Herman, J.P., Malluche, H.H., Koszewski, N.J., 2001. Evidence of functional vitamin D receptors in rat hippocampus. Neuroscience 104, 49–56.

Maldjian, J.A., Laurienti, P.J., Kraft, R.A., Burdette, J.H., 2003. An automated method for neuroanatomic and cytoarchitectonic atlas-based interrogation of fMRI data sets. Neuroimage 19, 1233–1239.

McCann, J.C., Ames, B.N., 2008. Is there convincing biological or behavioral evidence linking vitamin D deficiency to brain dysfunction? FASEB J. 22, 982–1001.

McGrath, J., Saari, K., Hakko, H., Jokelainen, J., Jones, P., Jarvelin, M.R., Chant, D., Isohanni, M., 2004. Vitamin D supplementation during the first year of life and risk of schizophrenia: a Finnish birth cohort study. Schizophr. Res. 67, 237–245.

McGrath, J.J., Eyles, D.W., Pedersen, C.B., Anderson, C., Ko, P., Burne, T.H., Norgaard-Pedersen, B., Hougaard, D.M., Mortensen, P.B., 2010. Neonatal vitamin D status and risk of schizophrenia: a population-based case-control study. Arch. Gen. Psychiatry 67, 889–894.

Miller, B.J., Buckley, P., Seabolt, W., Mellor, A., Kirkpatrick, B., 2011. Meta-analysis of cytokine alterations in schizophrenia: clinical status and antipsychotic effects. Biol. Psychiatry 70, 663–671.

Mithal, A., Wahl, D.A., Bonjour, J.P., Burckhardt, P., Dawson-Hughes, B., Eisman, J.A., El-Hajj Fuleihan, G., Josse, R.G., Lips, P., Morales-Torres, J., 2009. Global vitamin D status and determinants of hypovitaminosis D. Osteoporos. Int. 20, 1807–1820.

Naveilhan, P., Neveu, I., Baudet, C., Funakoshi, H., Wion, D., Brachet, P., Metsis, M., 1996a. 1,25-Dihydroxyvitamin D3 regulates the expression of the low-affinity neurotrophin receptor. Mol. Brain Res. 41, 259–268.

Naveilhan, P., Neveu, I., Wion, D., Brachet, P., 1996b. 1,25-Dihydroxyvitamin D3, an inducer of glial cell line-derived neurotrophic factor. Neuroreport 7, 2171–2175.

Phang, J.M., Liu, W., Zabirnyk, O., 2010. Proline metabolism and microenvironmental stress. Annu. Rev. Nutr. 30, 441–463.

Rey-Sanchez, P., Lavado-Garcia, J.M., Canal-Macias, M.L., Gomez-Zubeldia, M.A., Roncero-Martin, R., Pedrera-Zamorano, J.D., 2009. Ultrasound bone mass in schizophrenic patients on antipsychotic therapy. Hum. Psychopharmacol. 24, 49–54.

Samuelsson, A.M., Jennische, E., Hansson, H.A., Holmang, A., 2006. Prenatal exposure to interleukin-6 results in inflammatory neurodegeneration in hippocampus with NMDA/GABA(A) dysregulation and impaired spatial learning. Am. J. Physiol. Regul., Integr. Comp. Physiol. 290, R1345–R1356.

Sheehan, D.V., Lecrubier, Y., Sheehan, K.H., Amorim, P., Janavs, J., Weiller, E., Hergueta, T., Baker, R., Dunbar, G.C., 1998. The Mini-International Neuropsychiatric Interview (M.I.N.I.): the development and validation of a structured diagnostic

Please cite this article as: Shivakumar, V., et al., Serum vitamin D and hippocampal gray matter volume in schizophrenia. Psychiatry Research: Neuroimaging (2015), http://dx.doi.org/10.1016/j.pscychresns.2015.06.006

psychiatric interview for DSM-IV and ICD-10. J. Clin. Psychiatry 59 (Suppl. 20), 22–23 (quiz 34–57).
Steen, R.G., Mull, C., McClure, R., Hamer, R.M., Lieberman, J.A., 2006. Brain volume in first-episode schizophrenia: systematic review and meta-analysis of magnetic resonance imaging studies. Br. J.f Psychiatry 188, 510–518.
Suntsova, M., Gogvadze, E.V., Salozhin, S., Gaifullin, N., Eroshkin, F., Dmitriev, S.E., Martynova, N., Kulikov, K., Malakhova, G., Tukhbatova, G., Bolshakov, A.P., Ghilarov, D., Garazha, A., Aliper, A., Cantor, C.R., Solokhin, Y., Roumiantsev, S., Balaban, P., Zhavoronkov, A., Buzdin, A., 2013. Human-specific endogenous retroviral insert serves as an enhancer for the schizophrenia-linked gene PRODH. Proc. Natl. Acad. Sci. USA 110, 19472–19477.
Tzourio-Mazoyer, N., Landeau, B., Papathanassiou, D., Crivello, F., Etard, O., Delcroix, N., Mazoyer, B., Joliot, M., 2002. Automated anatomical labeling of activations in SPM using a macroscopic anatomical parcellation of the MNI MRI single-subject brain. Neuroimage 15, 273–289.
Wang, J.Y., Wu, J.N., Cherng, T.L., Hoffer, B.J., Chen, H.H., Borlongan, C.V., Wang, Y., 2001. Vitamin D(3) attenuates 6-hydroxydopamine-induced neurotoxicity in rats. Brain Res. 904, 67–75.
Wang, X., Michaelis, E.K., 2010. Selective neuronal vulnerability to oxidative stress in the brain. Front. Aging Neurosci. 2, 12.
Willis, A., Bender, H.U., Steel, G., Valle, D., 2008. PRODH variants and risk for schizophrenia. Amino Acids 35, 673–679.
Wion, D., MacGrogan, D., Neveu, I., Jehan, F., Houlgatte, R., Brachet, P., 1991. 1,25-Dihydroxyvitamin D3 is a potent inducer of nerve growth factor synthesis. J. Neurosci. Res. 28, 110–114.
Wu, J.Q., Kosten, T.R., Zhang, X.Y., 2013. Free radicals, antioxidant defense systems, and schizophrenia. Prog. Neuro-psychopharmacol. Biol. Psychiatry 46, 200–206.

Please cite this article as: Shivakumar, V., et al., Serum vitamin D and hippocampal gray matter volume in schizophrenia. Psychiatry Research: Neuroimaging (2015), http://dx.doi.org/10.1016/j.pscychresns.2015.06.006