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Research Paper

Raphe Nuclei Echogenicity and Diameter of Third Ventricle in Schizophrenia Measured by Transcranial Sonography

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ABSTRACT

Introduction: Serotonergic system hyperactivity at 5-HT2A receptors on glutamate neurons in the cerebral cortex is one of the pathways that is theoretically linked to psychosis. In addition to neurotransmitter dysfunction, volumetric studies have revealed the loss of cortical gray matter and ventricular enlargement in patients with schizophrenia, although there is no case-control research on patients with schizophrenia to evaluate echogenicity of raphe nuclei (RN) or diameter of the third ventricle (DTV). To address these issues, the present study assessed midbrain RN, as the main source of brain serotonin, and DTV, as an index of atrophy, by transcranial sonography (TCS) in a group of patients with schizophrenia.

Methods: Thirty patients with schizophrenia and 30 controls were assessed by TCS for RN echogenicity and DTV. TCS was done through a temporal bone window via a phased-array ultrasound using a 2.5 MHz transducer in a depth of 14-16 cm. RN echogenicity was assessed by a semi-quantitative visual scale and DTV was measured in the thalamic plane.

Results: Twenty-three patients (76.5%) and 15 controls (50 %) showed hypoechogenicity of RN, which was marginally significant (P=0.06). DTV was on average larger in the experimental group (0.388 cm vs 0.234 cm, P<0.001).

Conclusion: Increased DTV in patients with schizophrenia is consistent with previous neuroimaging findings. However, marginally lower echogenicity of midbrain RN on TCS in schizophrenia is a new finding that supports the serotonin hypothesis of schizophrenia.

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Highlights

• 30 patients with schizophrenia and 30 controls were assessed by TCS for RN echogenicity and diameter of the third ventricle (DTV).

• 23 patients (76.5%) and 15(50 %) controls showed hypoechogenicity of RN which was marginally significant (P=0.06)

• DTV was in average larger in the patient's group (0.388 cm vs 0.234 cm, P<0.001).

• Increased DTV in the patients with schizophrenia is consistent with previous neuroimaging findings

• Marginally lower echogenicity of midbrain RN on TCS in schizophrenia is a new finding that supports the serotonin hypothesis of schizophrenia.

Plain Language Summary

Schizophrenia is a disabling psychiatric disorder. Various neurotransmitters have a role in the pathophysiology of schizophrenia including Serotonin and dopamine. This study assessed the echogenicity of raphe nuclei (RN), as the main source of brain serotonin, and the diameter of the third ventricle (DTV), as an index of atrophy, by transcranial sonography (TCS) method in 30 patients with schizophrenia and 30 healthy controls. Based on the results, 23 patients (76.5%) and 15 controls (50%) showed decreased echogenicity of RN. There was a significant difference between the two groups in terms of the echogenicity of RN. Moreover, the DTV diameter was significantly larger in patients compared to controls.

1. Introduction

Schizophrenia is one of the most disabling psychiatric disorders, with a prevalence of 1% worldwide (Charlson et al., 2018). It is characterized by positive (e.g. delusion) and negative symptoms (e.g. social withdrawal), as well as cognitive deficits (Świtaj et al., 2012).

Research has implicated the dysfunction of various neurotransmitters in the pathophysiology of schizophrenia. Serotonin and dopamine are the major neurotransmitters that have been implicated in schizophrenia. Numerous studies have revealed alterations in GABA, glutamate, and norepinephrine neurotransmission in several brain regions in schizophrenia (Yang & Tsai, 2017).

According to the serotonin theory of psychosis, hyperfunctioning of cortical serotonin/5-hydroxytryptamine 5-HT2A is associated with psychosis, which leads to hyperactivation of 5-HT2A receptors on glutamate neurons. This over-activity can result in increased release of serotonin and/or increased expression of 5-HT2A receptors, which leads to glutamate release. The release of glutamate in the ventral tegmental area (VTA) might trigger the mesolimbic pathway, leading to extra dopamine in the ventral striatum, which eventually results in psychotic features (Stahl, 2018).

The main brain morphological abnormalities noticed in patients with schizophrenia include loss of cortical gray matter, decreased volume of the amygdala, hippocampus, the frontal and temporal lobes, and ventricular enlargement suggesting that in addition to neurotransmitter dysregulation, a neurodegenerative process is present in a subset of patients with schizophrenia, probably those with severe cognitive impairment (Barkataki et al., 2006; Lauer & Krieg, 1998; Lieberman et al., 2001; Pérez-Neri et al., 2006).

Transcranial parenchymal sonography (TCS) displays echogenicity of brain tissue through the intact skull and is a noninvasive, easily accessible, cost-effective, quickly applicable, and practical method to evaluate basal ganglia and midbrain structures, including raphe nuclei (RN) and diameter of third ventricle (DTV) and frontal horns of the lateral ventricles with a comparable resolution to magnetic resonance imaging (Walter et al., 2008).

Former TCS studies indicated reduced echogenicity of brainstem raphe (BR) in patients with major depression (Becker et al., 1994; Ghourchian et al., 2014; Zhang et al., 2016), depression associated with Parkinson's disease (Becker et al., 1997) and Wilson's disease (Walter et al., 2005) but not in healthy adults, bipolar affective disorder (Krogias et al., 2011), and multiple sclerosis with depression or geriatric

depression (Berg et al., 2000; Şenel et al., 2020). A previous study investigated echogenicity of the substantia nigra (SN) in different schizophrenic subforms by TCS amongst patients with schizophrenic spectrum psychoses treated with neuroleptic drugs, although there is no case-control research on patients with schizophrenia in order to evaluate echogenicity of RN or DTV (Jabs et al., 2001). Also, a review article suggested more investigations using this tool among patients with psychiatric disorders (Drepper et al., 2018). According to the serotonin hypothesis and the relatively similar pathogenesis of depression and schizophrenia, it can be considered to have same findings on raphe echogenicity.

In the present study, we evaluated the echogenicity of BR nuclei and DTV in a group of schizophrenia patients and compared them with healthy controls.

2. Material and methods

Subjects

Thirty patients with schizophrenia were selected from Iran Psychiatric Hospital and 30 control subjects of the same age and sex were enrolled from the hospital staff. Exclusion criteria for the case group were an acute phase of illness and other psychiatric comorbidities, like major depressive disorder, as well as poor temporal window for TCS. The control group was evaluated by a psychiatrist to rule out possible psychiatric disorders. Schizophrenia was diagnosed based on the diagnostic and statistical manual of mental disorders, fifth edition (DSM-5) (American Psychological Association, 2013).

Transcranial sonography

An experienced neurologist performed the TCS, who was blind to the diagnosis. We used a phased-array ultrasound system (Osnos 5500 Ultrasound System, Sonsite), with a 2.5 MHz probe (S3 probe) and penetration depth of 14-16 cm, through the temporal bone window in the midbrain plane for the assessment of BR and thalamic plane for measuring DTV. For the latter, we assessed the distance between the leading edges of the brain-ventricle interfaces in axial imaging planes. In the mesencephalic plane, the BR was recognized within the borders of the midbrain surrounded by the basal cisterns. RN echogenicity was graded as normal (continuous) and abnormal (non-continuous and absent)

Statistical analysis

SPSS software, version 18 was used to analyze the data. We calculated Mean±SD for quantitative and frequency percentages for qualitative variables. We used a chi-square test to compare decreased echogenicity between the two groups. In this study, we considered a type II error of less than 0.05 as significant.

3. Results

A total of 30 patients with schizophrenia and 30 controls participated in the study. The mean age of patients with schizophrenia and controls was 37.37±8.8 and 37.20±9.8 years, respectively (Table 1). In the case group, 23 patients showed decreased echogenicity of brainstem RN (76.5%), whereas, in the control group, only 15 individuals (50%) had a decreased echogenicity. There was a marginally significant difference between the two groups in terms of the echogenicity of RN (P=0.06).

Comparing the two groups for DTV, it was significantly higher in the case group, (0.388 cm vs 0.234 cm, P<0.001). Also, there was a significant correlation between age and DTV, with older participants having larger ventricles (P=0.003) (Figure 1).

Overall, DTV and age had a statistically significant correlation (P=0.003); however, when we investigated this correlation separately in patients and controls, although there still was a significant correlation between age and DTV in the case group (P=0.001), this correlation was not statistically significant in controls (P=0.091). Nonetheless, as is evident with the fit lines in Figure 1, in both groups, older people tended to have larger DTVs.

4. Discussion

Ultrasound (US) imaging may provide biomarkers and therapeutic options for psychiatric disorders. TCS is useful in determining vascular, structural, and functional brain changes in mental disorders. Some studies have shown changes in BR echogenicity with TCS in psychiatric disorders (Siragusa et al., 2020). We assessed BR nuclei and DTV in patients with schizophrenia as representatives of the serotonin system and brain atrophy, respectively.

As far as we know, this is the first study evaluating RN echogenicity and DTV in patients with schizophrenia using TCS. The results revealed no significant BR echogenicity change in patients with schizophrenia compared to the healthy control group; however, DTV increased.

In this study, the sample size was small and the p-value was borderline (P=0.06); thus, the results may not be representative of patients with schizophrenia and indicates the necessity of further investigations with larger sample sizes.

Table 1. Comparison of transcranial sonography findings in schizophrenia patients and control group

Variables		Mean±SD/No. (%)		P
		SCZ (n=30)	HC (n=30)	
Sex	Male Female	≥8 ≥22	≥8 ≥22	Matched
Age (y)		37.3±8.8	37.2±9.8	0.945
Brainstem raphe echogenicity	Normal	7(23.3)	15(50)	0.06
Reduced		23(26.6)	15(50)	
3rd ventricle (cm)		0.38	0.23	<0.001

SCZ: Schizophrenia; HC: Healthy control.

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It should be noted that several studies have revealed decreased echogenicity of BR nuclei in depressive disorders (Ghourchian et al., 2014). It seems that hypoechogenicity of BR in major depression is related to basal limbic system dysfunction; however, the exact etiology of altered echogenicity of brainstem RN is not still clear. The decreased echogenicity of the brainstem RN in TCS may reflect the decreased level of serotonin in major depressed patients (Ghourchian et al., 2014). The better response of depressed patients with hypoechogenicity of the brainstem RN to selective serotonin reuptake inhibitors (SSRIs) may support this hypothesis as well (Walter et al., 2007).

The serotonin hypothesis of psychosis in schizophrenia is somewhat different from that of major depressive disorder. Psychosis can be associated with hyperactivation of 5-HT2A receptors on glutamate neurons. This hyperactivation may be caused by excess serotonin, upregulated 5-HT2A receptors, or a psychedelic hallucinogenic 5-HT2A agonist (Carhart-Harris et al., 2016), which all can result in a decrease in glutamate. The release of glutamate in the ventral tegmental area activates the mesolimbic dopamine pathway in turn and results in psychosis (Ghajar et al., 2018; Stahl, 2018). Considering the different serotonergic disorders in depression and schizophrenia, it is logical to obtain different results from an ultrasound examination of the RN in these two entities.

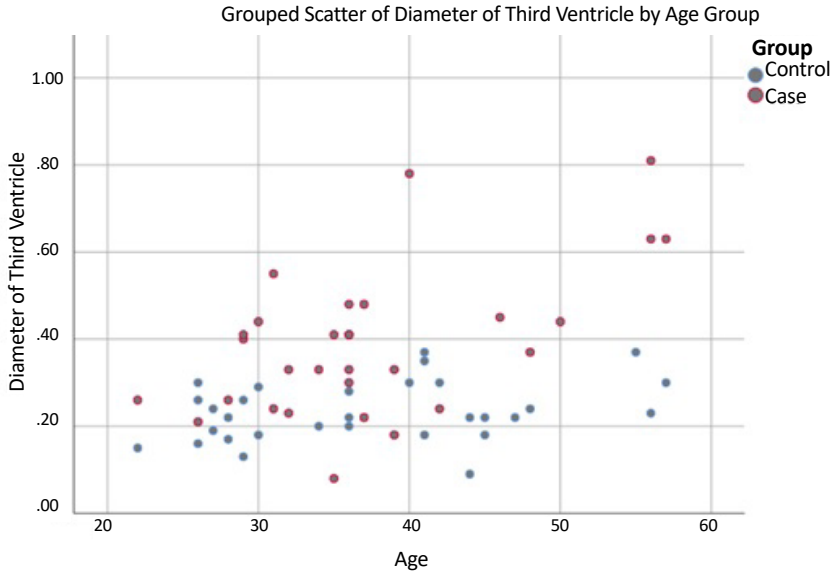

Figure 1. Simple scatter with fit line of diameter of third ventricle by age.

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Positive symptoms of psychosis are attributable to dopamine excess in the mesolimbic pathway. Therefore, we expect that blockade of dopamine D2 receptors result in treatment. However, antagonism of 5HT2A (without D2 antagonism) has shown acceptable antipsychotic effects in patients with Parkinson's disease, and some preliminary evidence for efficacy exists in patients with psychosis and dementia (Stahl, 2016).

In addition, dysregulation of the serotonin system plays a major role in the etiology of obsessive-compulsive disorder (OCD). Changes in the serotonergic brainstem RN have been shown in major depressive disorder and depressed patients with Parkinson's disease and Huntington's disease. Although decreased echogenicity of midbrain RN is observed in patients with major depressive disorder, it has been reported in patients with OCD, which can be explained by the involvement of RN projections rather than RN serotonergic neurons (Mohammadzade et al., 2018).

Another finding of this study was a larger DTV of patients with schizophrenia. Şenel et al. reported increased DTV measured by TCS in geriatric depression (Şenel et al., 2020). Ventricular enlargement is apparent in patients with chronic schizophrenia but is not a feature at the earliest stages of the illness (Berger et al., 2017).

Regarding the pathophysiology of schizophrenia, neurodevelopmental and neurodegenerative theories are the most popular and there are studies supporting the role of both mechanisms together (Berger et al., 2017). Longitudinal cohort studies on patients with schizophrenia have revealed a progressive loss of cerebral grey matter, more apparent in the frontal and temporal lobes (Dell'Osso et al., 2018).

The main brain morphological abnormalities observed in patients with schizophrenia are loss of cortical gray matter, decreased volume of the amygdala, hippocampus, frontal and temporal lobes, and ventricular enlargement (Pérez-Neri et al., 2006). In addition, our findings showed that DTV is significantly correlated with age in both groups, which is consistent with other studies using TCS among patients with other neurodegenerative neuropsychiatric disorders (Almasi-Dooghaee et al., 2021). Therefore, our results are consistent with previous findings that brain atrophy reflects some possible neurodegenerative processes in schizophrenia.

Limitations of the present study are the lack of other neuroimaging techniques, such as magnetic resonance imaging (MRI), and the small sample size. We recommend considering these points for future studies.

5. Conclusion

Increased DTV in patients with schizophrenia is consistent with previous neuroimaging findings. However, marginally lower echogenicity of midbrain RN on TCS in schizophrenia is a new finding that supports the serotonin hypothesis of schizophrenia. Further studies are required in this regard.

Ethical Considerations

Compliance with ethical guidelines

The Ethics Committee of the Iran University of Medical Sciences (Code: IRB: IR.IUMS.REC1394.8821215225) approved the study. We performed the study according to the Declaration of Helsinki, and received written informed consent from all participants.

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Authors' contributions

Conceptualization and study design: Mahnoush Mahdiar, Seyed Vahid Shariat, Babak Zamani and Mohammad Rohani; Data collection: Mahnoush Mahdiar, Fahimeh Haji Akhoundi, Fatemeh Kashaninasab, Babak Zamani, Seyed Vahid Shariat, Mohammadreza Shalbafan and Mohammad Rohani; Data interpretion and data analysis: Seyed Vahid Shariat and AmirSina Homayooni; Mahnoush Mahdiar, Nahid Mohammadzade, AmirSina Homayooni, Mohammadreza Shalbafan and Mohammad Rohani; Fianl approval: All authors.

Conflict of interest

The authors declared no conflict of interest.

References

Almasi-Dooghaee, M., Rohani, M., Imani, A., Nadjafi, S., & Zamani, B. (2021). The role of transcranial sonography in differentiation of dementia subtypes: An introduction of a new diagnostic method. *Neurological Sciences, 42*(1), 275-283. [DOI:10.1007/s10072-020-04566-4] [PMID]

Barkataki, I., Kumari, V., Das, M., Taylor, P., & Sharma, T. (2006). Volumetric structural brain abnormalities in men with schizophrenia or antisocial personality disorder. *Behavioural Brain Research, 169*(2), 239-247. [DOI:10.1016/j.bbr.2006.01.009] [PMID]

Becker, G., Struck, M., Bogdahn, U., & Becker, T. (1994). Echogenicity of the brainstem raphe in patients with major depression. *Psychiatry Research, 55*(2), 75-84. [DOI:10.1016/0925-4927(94)90002-7] [PMID]

Becker, T., Becker, G., Seufert, J., Hofmann, E., Lange, K. W., & Naumann, M., et al. (1997). Parkinson's disease and depression: evidence for an alteration of the basal limbic system detected by transcranial sonography. *Journal of Neurology, Neurosurgery & Psychiatry, 63*(5), 590-595. [DOI:10.1136/jnnp.63.5.590] [PMID]

Berg, D., Supprian, T., Thomae, J., Warmuth-Metz, M., Horowski, A., & Zeiler, B., et al. (2000). Lesion pattern in patients with multiple sclerosis and depression. *Multiple Sclerosis Journal, 6*(3), 156-162. [PMID]

Berger, G. E., Bartholomeusz, C. F., Wood, S. J., Ang, A., Phillips, L. J., & Proffitt, T., et al. (2017). Ventricular volumes across stages of schizophrenia and other psychoses. *Australian & New Zealand Journal of Psychiatry, 51*(10), 1041-1051. [DOI:10.1177/0004867417715914] [PMID]

Carhart-Harris, R. L., Muthukumaraswamy, S., Roseman, L., Kaelen, M., Droog, W., & Murphy, K., et al. (2016). Neural correlates of the LSD experience revealed by multimodal neuroimaging. *Proceedings of the National Academy of Sciences of the United States of America, 113*(17), 4853-4858. [DOI:10.1073/pnas.1518377113] [PMID]

Charlson, F. J., Ferrari, A. J., Santomauro, D. F., Diminic, S., Stockings, E., & Scott, J. G., et al. (2018). Global epidemiology and burden of schizophrenia: Findings from the global burden of disease study 2016. *Schizophrenia Bulletin, 44*(6), 1195-1203. [DOI:10.1093/schbul/sby058] [PMID]

Dell'Osso, Bernardo, Palazzo, M Carlotta, & Altamura, A Carlo. (2018). Neurodevelopmental and neurodegenerative alterations in the pathophysiology of schizophrenia: Focus on neuro-immuno-inflammation Neurodegenerative Diseases (pp. 337-348). Berlin: Springer. [Link]

Drepper, C., Geißler, J., Pastura, G., Yilmaz, R., Berg, D., & Romanos, M., et al. (2018). Transcranial sonography in psychiatry as a potential tool in diagnosis and research. *The World Journal of Biological Psychiatry, 19*(7), 484-496. [DOI:10.1080/15622975.2017.1386325] [PMID]

American Psychological Association. (2013). Diagnostic and statistical manual of mental disorders. Washington, DC: American Psychological Association. [Link]

Ghajar, A., Khoaie-Ardakani, M. R., Shahmoradi, Z., Alavi, A. R., Afarideh, M., & Shalbafan, M. R., et al. (2018). L-carnosine as an add-on to risperidone for treatment of negative symptoms in patients with stable schizophrenia: A double-blind, randomized placebo-controlled trial. *Psychiatry Research, 262,* 94-101. [DOI:10.1016/j.psychres.2018.02.012] [PMID]

Ghourchian, S., Zamani, B., Poorkosary, K., Malakouti, S. K., & Rohani, M. (2014). Raphe nuclei echogenicity changes in major depression. *Medical Journal of The Islamic Republic of Iran, 28,* 9. [PMID]

Jabs, B. E., Berg, D., Merschdorf, U., Bartsch, A. J., & Pfuhlmann, B. (2001). Differences in substantia nigra echogenicity of nosological subtypes within the schizophrenic spectrum. A preliminary transcranial ultrasound study. *Neuropsychobiology, 44*(4), 183-186. [DOI:10.1159/000054940] [PMID]

Krogias, C., Hoffmann, K., Eyding, J., Scheele, D., Norra, C., & Gold, R., et al. (2011). Evaluation of basal ganglia, brainstem raphe and ventricles in bipolar disorder by transcranial sonography. *Psychiatry Research, 194*(2), 190-197. [DOI:10.1016/j.pscychresns.2011.04.002] [PMID]

Lauer, C. J., & Krieg, J. C. (1998). Slow-wave sleep and ventricular size: A comparative study in schizophrenia and major depression. Biological Psychiatry, 44(2), 121-128. [DOI:10.1016/S0006-3223(97)00342-9] [PMID]

Lieberman, J., Chakos, M., Wu, H., Alvir, J., Hoffman, E., & Robinson, D., et al. (2001). Longitudinal study of brain morphology in first episode schizophrenia. *Biological Psychiatry, 49*(6), 487-499. [DOI:10.1016/S0006-3223(01)01067-8] [PMID]

Mohammadzade, N., Shalbafan, M. R., Shariat, S. V., Zamani, B., Shariati, B., & Omrani, F., et al. (2018). Raphe nuclei echogenicity changes in obsessive-compulsive disorder. *Medical Journal of The Islamic Republic of Iran, 32,* 91. [DOI:10.14196/mjiri.32.91] [PMID]

Pérez-Neri, I., Ramírez-Bermúdez, J., Montes, S., & Ríos, C. (2006). Possible mechanisms of neurodegeneration in schizophrenia. *Neurochemical Research, 31*(10), 1279-1294. [DOI:10.1007/s11064-006-9162-3] [PMID]

Şenel, B., Özel-Kızıl, E. T., Sorgun, M. H., Tezcan-Aydemir, S., & Kırıcı, S. (2020). Transcranial sonography imaging of brainstem raphe, substantia nigra and cerebral ventricles in patients with geriatric depression. *International Journal of Geriatric Psychiatry, 35*(7), 702–711. [DOI:10.1002/gps.5287] [PMID]

Siragusa, M. A., Réméniéras, J. P., Bouakaz, A., Escoffre, J. M., Patat, F., & Dujardin, P. A., et al. (2020). A systematic review of ultrasound imaging and therapy in mental disorders. *Progress in Neuro-Psychopharmacology and Biological Psychiatry, 101,* 109919. [DOI:10.1016/j.pnpbp.2020.109919] [PMID]

Stahl S. M. (2016). Parkinson's disease psychosis as a serotonin-dopamine imbalance syndrome. *CNS Spectrums, 21*(5), 355-359. [DOI:10.1017/S1092852916000602] [PMID]

Stahl S. M. (2018). Beyond the dopamine hypothesis of schizophrenia to three neural networks of psychosis: Dopamine, serotonin, and glutamate. *CNS Spectrums, 23*(3), 187-191. [DOI:10.1017/S1092852918001013] [PMID]

Świtaj, P., Anczewska, M., Chrostek, A., Sabariego, C., Cieza, A., & Bickenbach, J., et al. (2012). Disability and schizophrenia: A systematic review of experienced psychosocial difficulties. *BMC Psychiatry, 12,* 193. [DOI:10.1186/1471-244X-12-193] [PMID]

Walter, U., Krolikowski, K., Tarnacka, B., Benecke, R., Czlonkowska, A., & Dressler, D. (2005). Sonographic detection of basal ganglia lesions in asymptomatic and symptomatic Wilson disease. *Neurology, 64*(10), 1726-1732. [DOI:10.1212/01.WNL.0000161847.46465.B9] [PMID]

Walter, U., Kanowski, M., Kaufmann, J., Grossmann, A., Benecke, R., & Niehaus, L. (2008). Contemporary ultrasound systems allow high-resolution transcranial imaging of small echogenic deep intracranial structures similarly as MRI: A phantom study. *Neuroimage, 40*(2), 551-558. [DOI:10.1016/j.neuroimage.2007.12.019] [PMID]

Walter, U., Prudente-Morrissey, L., Herpertz, S. C., Benecke, R., & Hoeppner, J. (2007). Relationship of brainstem raphe echogenicity and clinical findings in depressive states. *Psychiatry Research, 155*(1), 67–73. [DOI:10.1016/j.pscychresns.2006.12.001] [PMID]

Yang, A. C., & Tsai, S. J. (2017). New targets for schizophrenia treatment beyond the dopamine hypothesis. *International Journal of Molecular Sciences, 18*(8), 1689. [DOI:10.3390/ijms18081689] [PMID]

Zhang, Y. C., Hu, H., Luo, W. F., Sheng, Y. J., Chen, X. F., & Mao, C. J., et al. (2016). Alteration of brainstem raphe measured by transcranial sonography in depression patients with or without Parkinson's disease. *Neurological Sciences, 37*(1), 45-50. [DOI:10.1007/s10072-015-2350-7] [PMID]

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