مجلة الدراسات التربوية والعلمية - كلية التربية - الجامعة العراقية
العدد الثالث والعشرون - المجلد الثالث - علم النفس - آذار 2024 م
doi.org/10.52866/esj.2023.03.23.19

A review article:
The Potential Role of Anemia in the Incidence of Schizophrenia

Abbas S. Neamah[1], Rana H. K. Al-Rubaye [2], Fadhel Molammed Lafta [1]
[1]Dept of Biology, College of Science, University of Baghdad, Baghdad, Iraq.
[2] Department of Biology, College of Education for Pure Sciences, Ibn Al-Haitham, University of Baghdad, Iraq.

Abstract:

Schizophrenia (ZP) is a common devastating cognitive disorder; however, the etiology of its incidence remains largely unclear yet. Although some evidence blames both environment and genetic factor as main drivers of ZP, but the clear mechanism of their effect elusive till now. Of interest, severe anemia conditions can lead to hypoxia in CNS which disturbs the normal structures and functions of some area in the brain resulting in abnormalities in the neurons communications and decrease synaptic plasticity. Additionally, modulation of cytoskeleton constituents is thought to participate to ZP development. Recently, it has been revealed that iron deficiency, which is the main cause of anemia, has a significant impact on the cytoskeleton constituent's disassembly. Such conditions are believed to evoke responses to adaptive as increase some neurotransmitter such as dopamine, which in turn exacerbates the disease pathophysiology events. Accordingly, the purpose of this review to provide an insight to the potential impact of anemia on ZP development.

Keywords: Schizophrenia, anemia, hypoxia, BDNF, neurons' cytoskeleton .

دراسة مراجعة :
الدور المحتمل لفقر الدم في حدوث فصام الشخصية

عباس سعد نعمة [1] ، رنا حنان خضير الربيعي [2] ، فاضل محمد لفته[1]
[1] قسم علوم الحياة، كلية العلوم جامعة بغداد ، بغداد ، العراق
[2] قسم علوم الحياة، كلية التربية للعلوم الصرفة ، ابن الهيثم، جامعة بغداد، بغداد ، العراق

مستخلص:

فصام الشخصية (ZP) هو اضطراب إدراكي مدمر شائع. ومع ذلك، فإن اسباب حدوثه لا تزال غير واضحة إلى حد كبير حتى الآن. على الرغم من وجود بعض الأدلة التي تشير الى دور البيئة والعامل الوراثي كمسببين رئيسيين لمرض ZP، إلا أن الآلية الواضحة لتأثيرهما غير واضحة حتى الآن. ومن المثير للاهتمام أن حالات فقر الدم الشديدة يمكن أن تؤدي إلى نقص الأوكسجين في الجهاز العصبي المركزي مما يؤثر على التركيب والوظائف الطبيعية لبعض المناطق في الدماغ مؤديا إلى خلل في اتصالات الخلايا العصبية وانخفاض المرونة الاشتباكية. بالإضافة إلى ذلك، يُعتقد أن التغيرات في بُنية الهيكل الخلوي يمكن ان تساهم في تطوير ZP وقد تبين مؤخراً أن نقص الحديد، وهو السبب الرئيسي لفقر الدم، له تأثير كبير على تفكيك مكونات الهيكل الخلوي. كما يُعتقد أن مثل هذه الحالات تثير استجابات تكيفية مثل زيادة بعض النواقل العصبية كالدوبامين، والذي بدوره يؤدي إلى تفاقم أحداث الفيزيولوجيا المرضية. وبناء على ذلك، فإن الغرض من هذه المراجعة هو تقديم نظرة شاملة لزيادة فهم التأثير المحتمل لفقر الدم في نشؤ وتطور مرض فصام الشخصية.

الكلمات المفتاحية : فصام الشخصية، فقر الدم، نقص الاوكسجين، BDNF ، الهيكل الخلوي للاعصاب.

Introduction:

Schizophrenia is a devastating mental illness results in a dysfunctional lifestyle. It causes social withdrawal, cognitive impairment, and decreased emotional reflection [1-3]. There are no diagnostic tools to detect schizophrenia; diagnosis is depended on behavior observed. This means that the disease cannot be predicted, but rather diagnosed after the symptoms are resulting from damage certain areas in the brain [4]. The global incidence of schizophrenia ranges between 3 to 7.0%, with globally twenty-four million affected cases according to the WHO statistics [5]. Several studies have been shown the higher rate of suicide action in people diagnosed with schizophrenia [6-7]. However, the etiology of schizophrenia is still unclear, but in general it is believed that environment and genetic variations are considered to have involvement in the occurrence of ZP [8].

What is not yet clear is the potential involvement of anemia as a risk factor in schizophrenia. A number of studies have found increased prevalence anemia among patients with schizophrenia [9]. One of the potential effects of anemia on the CNS is a change in the neuron cytoskeleton, which alters neuronal synapses [10]. Recent evidences suggest the schizophrenia could be related to impaired neuronal connecting caused by abnormality in the shape of the neuron axon [11]. Postmortem studies in schizophrenia have illustrated the most of dysfunctions is consequences of the disturbance in axonal synaptic [12]. Impairment of axonal synapses is the result of poorly performing oligodendrocytes and cells producing myelin. These circumstances increase dopamine secretion as a mechanism to speeding the signaling transmission in the context of axonal connections abnormalities [13].

Severe anemia led to hypoxia in the CNS, and this in turn resulted in elevated levels of hypoxia-inducible factor-1 alpha (HIF-1α). Under these circumstance miR-210-3p is activated, which suppressing the brain-derived neurotrophic factor (BDNF) [14-15], Furthermore, numerous studies shown the hypoxia can be blocking and alter BDNF intercellular signaling pathway (Fig.1) [16, 17]. The most important relevant roles of BDNF in CNS are enhancing the differentiation of oligodendrocyte precursor cells (OPCs). Addi-

tionally, BDNF controls local translation of neuronal proteins, as well as regulates of cytoskeleton and membrane dynamics [18]. Furthermore, pathophysiologic link between schizophrenia and perturbed cortical iron biology has been suggested recently[19].

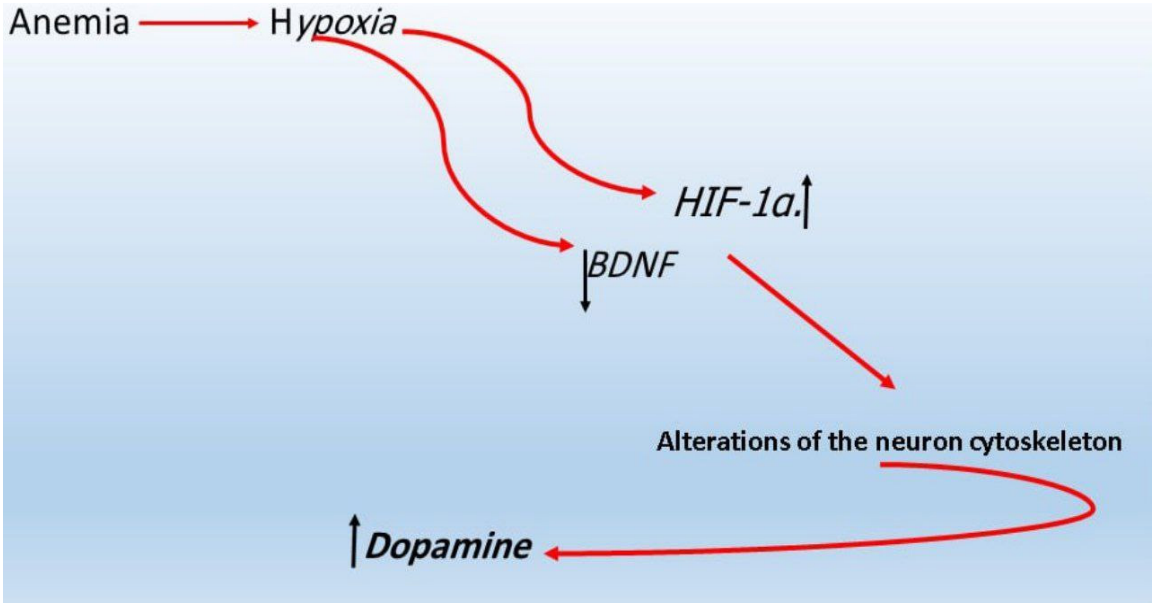

Figure1: The potential underlying effect of anemia in schizophrenia

Effect of anemia on the neuron cytoskeleton via *BDNF* expression modulation

Anemia is state characterized by a lessening the number of erythrocyte, or reduce the quantity of hemoglobin in the blood results to a decrease the capacity of oxygen-carrying [20-22]. The brain responds to the severe chronic anemia via activation the expression of HIF-1α[4]<. HIF-1α plays crucial role in *BDNF* suppression via direct binding to its promoter region leading to reduced levels of BDNF [23]. Additionally, hypoxia can impair the *BDNF* expression through down regulation of its transcription factors such as REST (RE-1 Silencing Transcription factor), which plays important role in upregulation of *BDNF* gene [24]. Furthermore, hypoxia circumstances promote the enzymatic activity of BACE1 (β-site amyloid precursor protein cleaving enzyme 1) that is involved in the degradation of BDNF (Fig.2) [25].

The evidence presented thus far supports the idea that hypoxia can lead to inflammation in CNS [26]. Most studies in this field have found a significantly negative correlation between hypoxia status and *BDNF* expression in neurons. It is identified that hypoxia can cause epigenetic alternations in *BDNF* gene, via increase DNA methylation at specific CpG within promoter of *BDNF* gene, which in turn, reduced or silence the BDNF mRNA [27].

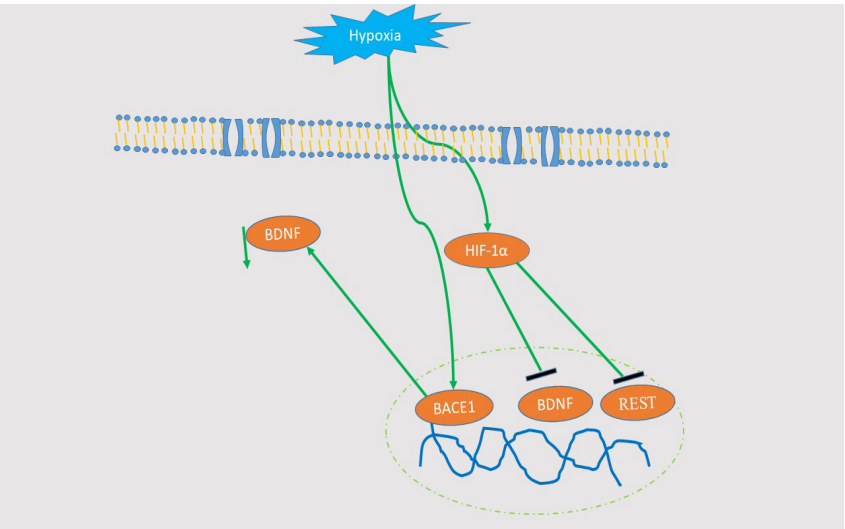

Figure 2: Signaling pathway of under hypoxia circumstance. Hypoxia cause upregulation HIF-a, which in turn downregulation *BDNF*, as well as downregulation *REST* which in turn upregulation *BDNF*. Additionally, hypoxia activation *BACE1* which is plays role in degradation of *BDNF*

As it mentioned earlier, BDNF plays crucial in the neuroplasticity, which means losing the ability of the brain to form new neurons connection if there are any impaired in *BDNF* expression [28]. Additionally, *BDNF* maintain the synaptic modulation and reduced its levels can cause decrease in neuron communication [29]. Furthermore, recent studies have illustrated that any alternation in neuron plasticity can increased dopamine secretion [30]. On the other hand, recent investigations have shown that BDNF induce oligodendrocyte precursor cells (OPC) survival, proliferation and differentiation [31]. There is a large volume of published studies describing the role of oligodendrocyte in maintaining the neuron cytoskeleton, via specific factors expression such as adhesion molecules [32]. As well as growth factors and signaling molecules that enhance organization the neuron cy-

toskeleton, while the signaling molecules influences on the cytoskeleton components through assemble and disassemble, such as actin and microtubule [33]. Furthermore, oligodendrocyte considerable main source for myelin sheet, which in turn important to neuron synapse [34]. Recent studies have been investigated the potential mechanism underlying schizophrenia, where it found the alternation in OPCs, such as disturbance of differentiation and myelination of OPC implicated in many cognitive disorder [35].

Effect of anemia on the neuron cytoskeleton via the regulation of actin dynamics

Actin dynamics demonstrate important role in the neuron communication, and development. Previous studies have shown that actin dynamics involved in axonal guidance in a neuron synaptic, as well as, do crucial job in synaptic plasticity *via* regulating the stability and strength of synapses [36]. Moreover, actin dynamics are considered as principal factor in synapse formation by stabilizing the structure of dendritic spines [37]. Furthermore, polymerization and remodeling of actin contribute to long term depression (LTD) and long term potentiation (LTP) [38], where a number of studies have reported that patients with schizophrenia presented both of the aforementioned abnormalities. The LTP in hippocampus of patients with schizophrenia is reduced compared to their healthy counterparts, and it was correlated with dyscognitive in the schizophrenic patients [39]. Another study investigated the normality of LTP in the hippocampus showed there is more decrease in function of LTP in schizophrenia patients, in comparison to healthy individuals[40] .

Increasingly evidence suggest that hypoxia have indirectly impact on adrenergic system in the ventral tegmental area (VTA) via disruption of actin filament, which results in alternation in neuron cytoskeleton [41]. On the other hand, hypoxia status triggers stress in the VTA, which could lead to the disturbance in actin filaments, resulting in alterations in synapse of adrenergic system[42]. Numerous studies confirmed the hypoxia circumstance leading to negative effects on the actin dynamics, via HIF which is activated in response to hypoxia status. Such HIF serves as a transcription factor regulates the expression some protein implicated in actin dynamic, such as, ROCK, cofilin,

and RhoA. These proteins involved in actin organization, polymerization, and actin cytoskeleton[43] . Recent research has shown there is abnormalities in ROCK signaling in patients with schizophrenia, that indicates potential role of ROCK signaling in schizophrenia[44] . Other studies are also shown, there is positive correlation among aberrant Rho GTPase and the disorders in the brain connectivity in individuals with schizophrenia [45].On the other hand, hypoxia can promote several signaling pathway, which influences on the remolding the actin dynamics, such as, the MAPK pathway, and PI3K/ Akt [46].

Recently, chronic anemias resulted from deficient iron delivery can damage the cytoskeletal framework of hematopoietic progenitor cells suggesting the identifying of targeted strategy for cytoskeletal repair, leading to anemia correction [47]. Additionally several lines of evidence have highlighted the involvement a number of schizophrenia-associated genes (and their encoded proteins) in modulating cytoskeleton constituents of nerve cells that is believed to involve in schizophrenia development. Such findings are summarized in Table 1.

Table1: Genes implicated in both cytoskeleton constituents' modulation and schizophrenia development.

Gene	**Potential impact in cytoskeleton modulation that linked to schizophrenia development**	**Refs**
DISC1	Directs microtubule network formation and microtubule organizing centre.	[48]
RTN4R	Regulation of actin cytoskeleton by Rho GTPases and the reorganization of actin cytoskeleton.	[49]
SYN2	Neuronal phosphoprotein covering synaptic vesicles, binds to the cytoskeleton, and regulates the release of neurotransmitter.	[50]
SHANK3	Structural and functional organization of the dendritic spine and synaptic junction plasticity.	[51]
DTNBP1	Plays a role in actin cytoskeleton reorganization and neurite outgrowth.	[52]
ULK4	Regulates neurite branching and elongation via remodeling of cytoskeletal constituents, including alpha-tubulin.	[53]
DLGAP2	An adapter protein linking ion channel to the subsynaptic cytoskeleton regulating and neuronal cell signaling.	[54]
MFAP5	Affect permeability and motility of endothelial cells via cytoskeleton rearrangement.	[55]

Gene	Potential impact in cytoskeleton modulation that linked to schizophrenia development	Refs
HECW2	Involved in the regulation of mitotic metaphase/anaphase transition.	[56]
KATNAL2	Major catalytic subunits of the microtubule-severing enzyme	[57]
BIRC6	Cytoskeleton and microtubules regulator	[58]
GRIN2B	Involves in actin cytoskeleton dynamics	[59]
AKT1	Phosphorylates palladin (PALLD), modulating cytoskeletal organization	[60]

Anemia (iron deficiency) as a risk factor for schizophrenia through neurotransmitter pathway

Iron is the most prevalent transition metal in the brain and is essential for many neurological processes, such as neurogenesis, axon myelination, synaptic development, mitochondrial function, electron transport, neurotransmitter synthesis, and metabolism [61]. Indeed, the disruption of iron homeostasis may influence neurophysiological mechanisms, cognition, and social behavior, ultimately contributing to the development of a wide range of neuropathologies [62]. Iron deficiency (ID) is the most common, avoidable, and treatable cause of anemia in the world [63-65]. Recent research suggests that neurotransmitters such as dopamine, glutamate, γ-aminobutyric acid GABA and serotonin are major contributors to schizophrenia, with dopamine playing the most important role [66]. According to the findings of a recent study [67] iron deficiency results in an alterations of monoamine neurotransmitters. Furthermore, dopamine (DA) is a key monoamine neurotransmitter in the brain that plays critical roles in higher brain activities such as motivation, reward, and cognitive function. Therefore, it is not surprising that dopaminergic signaling defects have been linked to the pathophysiology of several mental diseases, including attention deficit/hyperactivity disorder (ADHD), Huntington's disease (HD), Parkinson's disease (PD), and schizophrenia [68]. Moreover, iron is a cofactor of tyrosine hydroxylase, the rate-limiting enzyme in dopamine production. Therefore, it seems sense that decreased brain iron levels would decrease the availability of iron in dopamine neurons, which may therefore decrease dopamine activity in the central

nervous system. Reduced dopamine activity has been reported to be related to negative symptoms in schizophrenia patients [69].

On the other hand, serotonin is a neurotransmitter involved in the regulation of mood, neuronal activity, and anxiety and iron is necessary for its synthesis [67, 70-71]. Decreased circulating iron leads to disruption of serotonin metabolism and reduced serotonin levels [72]. Finally iron deficiency during pregnancy, as well as in infancy and childhood, is linked to motor, cognitive, and behavioral abnormalities that are like those seen in children who later develop schizophrenia [73 -75].

Conclusions

Considering the scarcity of evidence linked schizophrenia development to anemia and cytoskeleton constituents' disruption, a new insight can be gained by reviewing genes involved in regulating neural cell cytoskeleton in relation to the subsynaptic cytoskeleton regulating and neuronal cell signaling. Although the direct link between anemia and schizophrenia has not established yet, however, the potential link of iron deficiency to cytoskeleton dysregulation opens a new venue for understanding schizophrenia biology and suggesting novel therapeutic targets to tackle such devastating disease.

Funding

This review received no external funding.

Conflicts of Interest

The authors declare have no conflict of interest.

References:

1. Khudair, A. K., & Mohammed, Q. Q. (2014). Quality of Life in Schizophrenic Patients: The Relationship with Personal Characteristics. Iraqi National Journal of Nursing Specialties, 27(1).
2- Khudhiar, N. K., & Saud, A. M. (2019). Genetic Polymorphisms rs643627 in Serotonin Receptor Gene (5-HTR2A) with Schizophrenia. Iraqi Journal of Science, 2642-2648.
3. Alobaidi, Z. A., & Mohammed, S. I. (2023). Association of Disease Duration and Duration of Olanzapine Use with Blood Sugar, Blood Pressure, BMI, and Lipid Profile among Schizophrenic Patients in Iraq. *Al-Rafidain Journal of Medical Sciences (ISSN 2789-3219)*, *4*, 79-

85.

4. Shakir, A. S., Marzook, A. A., Kadim, J., Khalid, H., & Jassam, M. D. (2013). Sexual Dysfunctions among Male Schizophrenic Patients Attending Al-Rashad Sex Clinic. AL-Kindy College Medical Journal, 9(2), 21-24.
5. Scott, K. M., Lim, C., Al-Hamzawi, A., Alonso, J., Bruffaerts, R., Caldas-de-Almeida, J. M., & Kessler, R. C. (2016). Association of mental disorders with subsequent chronic physical conditions: world mental health surveys from 17 countries. JAMA psychiatry, 73(2), 150-158.
6. Bai, W., et al., *Worldwide prevalence of suicidal ideation and suicide plan among people with schizophrenia: a meta-analysis and systematic review of epidemiological surveys.* Translational psychiatry, 2021. **11**(1): p. 552.
7. Sher, L. and R.S. Kahn, *Suicide in schizophrenia: an educational overview.* Medicina, 2019. **55**(7): p. 361.
8. Frayyeh, A. H., & El-Saffar, J. M. J. (2015). Altered IL-2 and IL-10 serum levels in schizophrenic patients. Iraqi Journal of Science, 1932-1937.
9. Anuroj, K., S. Chongbanyatcharoen, and R. Chiencharoenthanakij, *Severe Anemia: A Case Report of an Uncommon Precipitant of Schizophrenia Relapse.* Journal of Blood Medicine, 2023: p. 329-336.
10. Perng, V., Li, C., Klocke, C. R., Navazesh, S. E., Pinneles, D. K., Lein, P. J., & Ji, P. (2021). Iron deficiency and iron excess differently affect dendritic architecture of pyramidal neurons in the hippocampus of piglets. The Journal of nutrition, 151(1), 235-244.
11. Dutta, T., *Megaloblastic Anemia.* Ann Clin Med Case Rep, 2023. **10**(15): p. 1-5.
12. Uranova, N., *The Neuropathology of White Matter in Schizophrenia.* The Neuropathology of Schizophrenia, 2021: p. 179-219.
13. Duncan, G.J., T.J. Simkins, and B. Emery, *Neuron-oligodendrocyte interactions in the structure and integrity of axons.* Frontiers in Cell and Developmental Biology, 2021. **9**: p. 653101.
14. Gattas, B. S., Ibetoh, C. N., Stratulat, E., Liu, F., Wuni, G. Y., Bahuva, R.,

& Gordon, D. K. (2020). The impact of low hemoglobin levels on cognitive brain functions. Cureus, 12(11).

15. Xie, Z., et al., *Perspectives on miRNAs directly targeting BDNF for cancer diagnosis and treatment.* International Journal of Oncology, 2023. **62**(2): p. 1-12.
16. Alder, J., Thakker-Varia, S., Bangasser, D. A., Kuroiwa, M., Plummer, M. R., Shors, T. J., & Black, I. B. (2003). Brain-derived neurotrophic factor-induced gene expression reveals novel actions of VGF in hippocampal synaptic plasticity. Journal of Neuroscience, 23(34), 10800-10808.
17. Zuccato, C., Liber, D., Ramos, C., Tarditi, A., Rigamonti, D., Tartari, M., & Cattaneo, E. (2005). Progressive loss of BDNF in a mouse model of Huntington's disease and rescue by BDNF delivery. Pharmacological research, 52(2), 133-139.
18. Popova, N.K. and V.S. Naumenko, *Neuronal and behavioral plasticity: The role of serotonin and BDNF systems tandem.* Expert opinion on therapeutic targets, 2019. **23**(3): p. 227-239.
19. Lotan, A., Luza, S., Opazo, C. M., Ayton, S., Lane, D. J., Mancuso, S., & Bush, A. I. (2023). Perturbed iron biology in the prefrontal cortex of people with schizophrenia. Molecular Psychiatry, 1-13.
20. Jafer, E. H., Attawi, J. A. A. J., & khudhur Mohammad, T. (2015). Relations between iron deficiency anemia and anemia from hookworms parasites. The Iraqi Journal of Veterinary Medicine, 39(2), 66-71.
21. Ma'ala, E. (2013). Assessment of Severity of Anemia Among Children Under 5 Years. *Iraqi National Journal of Nursing Specialties*, *26*(3), 9-14.
22. Al-Lami, M. Q., Al-Tai, Q. H., & Al-Ani, I. Y. (2011). Prevalence of Anemia among Iraqi Patients after Renal Transplantation. *Journal of the Faculty of Medicine Baghdad*, *53*(2), 121-125.
23. Wang, Z., Yang, D., Zhang, X., Li, T., Li, J., Tang, Y., & Le, W. (2011). Hypoxia-induced down-regulation of neprilysin by histone modification in mouse primary cortical and hippocampal neurons. PloS one, 6(4), e19229.

24 Licausi, F., Weits, D. A., Pant, B.

D., Scheible, W. R., Geigenberger, P., & van Dongen, J. T. (2011). Hypoxia responsive gene expression is mediated by various subsets of transcription factors and miRNAs that are determined by the actual oxygen availability. New phytologist, 190(2), 442-456.

25. Sun, X., He, G., Qing, H., Zhou, W., Dobie, F., Cai, F., & Song, W. (2006). Hypoxia facilitates Alzheimer's disease pathogenesis by up-regulating BACE1 gene expression. Proceedings of the National Academy of Sciences, 103(49), 18727-18732.
26. Asgarzadeh, A., Fouladi, N., Asgharіazar, V., Sarabi, S. F., Khiavi, H. A., Mahmoudi, M., & Safarzadeh, E. (2022). Serum Brain-Derived Neurotrophic Factor (BDNF) in COVID-19 Patients and its Association with the COVID-19 Manifestations. Journal of Molecular Neuroscience, 72(9), 1820-1830.
27. Jawahar, M. C., Murgatroyd, C., Harrison, E. L., & Baune, B. T. (2015). Epigenetic alterations following early postnatal stress: a review on novel aetiological mechanisms of common psychiatric disorders. Clinical epigenetics, 7(1), 1-13.
28. Wang, L., Liu, W., Zhang, Y., Hu, Z., Guo, H., Lv, J., & Du, H. (2020). Dexmedetomidine had neuroprotective effects on hippocampal neuronal cells via targeting lncRNA SHNG16 mediated microRNA-10b-5p/BDNF axis. Molecular and Cellular Biochemistry, 469, 41-51.
29. Wang, C.S., E.T. Kavalali, and L.M. Monteggia, *BDNF signaling in context: From synaptic regulation to psychiatric disorders.* Cell, 2022.
30. Volkow, N. D., Wang, G. J., Fowler, J. S., & Tomasi, D. (2012). Addiction circuitry in the human brain. Annual review of pharmacology and toxicology, 52, 321-336.
31. Zhai, Y., Wang, Q., Zhu, Z., Hao, Y., Han, F., Hong, J., & Cheng, G. (2022). High-efficiency brain-targeted intranasal delivery of BDNF mediated by engineered exosomes to promote remyelination. Biomaterials science, 10(19), 5707-5718.
32. Thornton, M.A. and E.G. Hughes, *Neuron-oligodendroglia interactions: Activity-dependent regulation of cellular signaling.* Neuroscience letters, 2020. **727**: p. 134916.

33. Buchanan, J., N.M. da Costa, and L. Cheadle, *Emerging roles of oligodendrocyte precursor cells in neural circuit development and remodeling.* Trends in Neurosciences, 2023.
34. Traiffort, E., Kassoussi, A., Zahaf, A., & Laouarem, Y. (2020). Astrocytes and microglia as major players of myelin production in normal and pathological conditions. Frontiers in Cellular Neuroscience, 14, 79.
35. Gouvêa-Junqueira, D., Falvella, A. C. B., Antunes, A. S. L. M., Seabra, G., Brandão-Teles, C., Martins-de-Souza, D., & Crunfli, F. (2020). Novel treatment strategies targeting myelin and oligodendrocyte dysfunction in schizophrenia. Frontiers in Psychiatry, 11, 379.
36. Zhou, F., Ouyang, L., Li, Q., Yang, S., Liu, S., Yu, H., & Fan, G. (2023). Hippocampal LIMK1-mediated Structural Synaptic Plasticity in Neurobehavioral Deficits Induced by a Low-dose Heavy Metal Mixture. Molecular Neurobiology, 60(10), 6029-6042.
37. Okabe, S., *Regulation of actin dynamics in dendritic spines: Nanostructure, molecular mobility, and signaling mechanisms.* Molecular and Cellular Neuroscience, 2020. **109**: p. 103564.
38. Pinho, J., C. Marcut, and R. Fonseca, *Actin remodeling, the synaptic tag and the maintenance of synaptic plasticity.* IUBMB life, 2020. **72**(4): p. 577-589.
39. Moghadam, A. A., Vose, L. R., Miry, O., Zhang, X. L., & Stanton, P. K. (2021). Pairing of neonatal phencyclidine exposure and acute adolescent stress in male rats as a novel developmental model of schizophrenia. Behavioural Brain Research, 409, 113308.
40. Zhan, J. Q., Chen, C. N., Wu, S. X., Wu, H. J., Zou, K., Xiong, J. W., & Yang, Y. J. (2021). Flavonoid fisetin reverses impaired hippocampal synaptic plasticity and cognitive function by regulating the function of AMPARs in a male rat model of schizophrenia. Journal of Neurochemistry, 158(2), 413-428.
41. Jain, R., Begum, N., Tryphena, K. P., Singh, S. B., Srivastava, S., Rai, S. N., & Khatri, D. K. (2023). Inter and intracellular mitochondrial transfer: future of mitochondrial transplant

therapy in Parkinson's disease. Biomedicine & Pharmacotherapy, 159, 114268.

42. Lana, D., F. Ugolini, and M.G. Giovannini, *An overview on the differential interplay among neurons–astrocytes–microglia in CA1 and CA3 hippocampus in hypoxia/ischemia.* Frontiers in cellular neuroscience, 2020. **14**: p. 585833.
43. Nevin, M., J. Gallego, and D.D. Eisenstat, *Axonal Guidance*, in *Neurodevelopmental Pediatrics: Genetic and Environmental Influences*. 2023, Springer. p. 93-106.
44. Hanifa, M., Singh, M., Randhawa, P., Jaggi, A. S., & Bali, A. (2023). A focus on Rho/ROCK signaling pathway: An emerging therapeutic target in depression. European Journal of Pharmacology, 175648.
45. Brakebusch, C., *Rho GTPase signaling in health and disease: a complex signaling network*. 2021, MDPI. p. 401.
46. Li, L., Lin, Z., Yuan, J., Li, P., Wang, Q., Cho, N., & Lin, Z. (2024). The neuroprotective mechanisms of naringenin: Inhibition of apoptosis through the PI3K/AKT pathway after hypoxic-ischemic brain damage. Journal of Ethnopharmacology, 318, 116941.
47. Goldfarb, A. N., Freeman, K. C., Sahu, R. K., Elagib, K. E., Holy, M., Arneja, A., & Delehanty, L. L. (2021). Iron control of erythroid microtubule cytoskeleton as a potential target in treatment of iron-restricted anemia. Nature Communications, 12(1), 1645.
48. Shimizu, S., Matsuzaki, S., Hattori, T., Kumamoto, N., Miyoshi, K., Katayama, T., & Tohyama, M. (2008). DISC1–kendrin interaction is involved in centrosomal microtubule network formation. Biochemical and biophysical research communications, 377(4), 1051-1056.
49. Wills, Z. P., Mandel-Brehm, C., Mardinly, A. R., McCord, A. E., Giger, R. J., & Greenberg, M. E. (2012). The nogo receptor family restricts synapse number in the developing hippocampus. Neuron, 73(3), 466-481.
50. Broek, J. A., Guest, P. C., Rahmoune, H., & Bahn, S. (2014). Proteomic analysis of post mortem brain tissue from autism patients: evidence for

opposite changes in prefrontal cortex and cerebellum in synaptic connectivity-related proteins. Molecular autism, 5(1), 1-8.

51. Peykov, S., Berkel, S., Schoen, M., Weiss, K., Degenhardt, F., Strohmaier, J., ... & Rappold, G. A. (2015). Identification and functional characterization of rare SHANK2 variants in schizophrenia. Molecular psychiatry, 20(12), 1489-1498.
52. Wang, H., Xu, J., Lazarovici, P., & Zheng, W. (2017). Dysbindin-1 involvement in the etiology of schizophrenia. International journal of molecular sciences, 18(10), 2044.
53. Luo, S., N. Zheng, and B. Lang, *ULK4 in Neurodevelopmental and Neuropsychiatric Disorders.* Frontiers in Cell and Developmental Biology, 2022. **10**: p. 873706.
54. Hsieh, M. Y., Tuan, L. H., Chang, H. C., Wang, Y. C., Chen, C. H., Shy, H. T., ... & Gau, S. S. F. (2023). Altered synaptic protein expression, aberrant spine morphology, and impaired spatial memory in Dlgap2 mutant mice, a genetic model of autism spectrum disorder. Cerebral Cortex, 33(8), 4779-4793.
55. Liu, P., Li, L., He, F., Meng, F., Liu, X., Su, Y., & Peng, G. (2023). Identification of candidate biomarkers of Alzheimer's disease via multiplex cerebrospinal fluid and serum proteomics. International Journal of Molecular Sciences, 24(18), 14225.
56. Kushima, I., et al., *Comparative analyses of copy-number variation in autism spectrum disorder and schizophrenia reveal etiological overlap and biological insights.* Cell reports, 2018. **24**(11): p. 2838-2856.
57. Banks, G., Lassi, G., Hoerder-Suabedissen, A., Tinarelli, F., Simon, M. M., Wilcox, A., & Nolan, P. M. (2018). A missense mutation in Katnal1 underlies behavioural, neurological and ciliary anomalies. Molecular psychiatry, 23(3), 713-722.
58. Dajani, R., Salah, T., Shbailat, S., Wei, Z., Daas, M., & Hakonarson, H. (2018). Genes associated with cancer, schizophrenia and type 2 diabetes in the circassian and Chechen populations in Jordan. Jordan Medical Journal, 52(1).
59. Kim, M. H., Kim, I. B., Lee, J., Park, S. M., Kim, J. H., Kim, R., & Lee, J. H. (2021). Low-level brain so-

matic mutations are implicated in schizophrenia. Biological Psychiatry, 90(1), 35-46.

60. Chadha, R., Alganem, K., Mccullumsmith, R. E., & Meador-Woodruff, J. H. (2021). mTOR kinase activity disrupts a phosphorylation signaling network in schizophrenia brain. Molecular psychiatry, 26(11), 6868-6879.

61. Nnah, I. C., & Wessling-Resnick, M. (2018). Brain iron homeostasis: a focus on microglial iron. Pharmaceuticals, 11(4), 129.

62. Ferreira, A., Neves, P., & Gozzelino, R. (2019). Multilevel impacts of iron in the brain: The cross talk between neurophysiological mechanisms, cognition, and social behavior. Pharmaceuticals, 12(3), 126

63. Muhealdeen, H. E. (2023). Effectiveness of Instruction Program on Adolescent Girls' Dietary Habits Diagnosed with Iron Deficiency Anemia. Iraqi National Journal of Nursing Specialties, 36(1).

64. PhDHematol, A. M. A. D., Al-Dulaimi, Y. H., & Al-Hamwandi, A. M. (2007). Iron Deficiency Anemia: The Utility of Upper Gastrointestinal Endoscopy and Histopathology. Al-Kindy College Medical Journal, 4(1).

65. Hassan, M. R. (2013). The prevalence of iron deficiency anemia among pregnant women in Ibn-Albaldy Hospital. Iraqi National Journal of Nursing Specialties, Vol. 26 (1).

66. Bansal, V., & Chatterjee, I. (2021). Role of neurotransmitters in schizophrenia: a comprehensive study. Kuwait Journal of Science, 48(2).

67. Lee, H. S., Chao, H. H., Huang, W. T., Chen, S. C. C., & Yang, H. Y. (2020). Psychiatric disorders risk in patients with iron deficiency anemia and association with iron supplementation medications: a nationwide database analysis. BMC psychiatry, 20, 1-9.

68. Klein, M. O., Battagello, D. S., Cardoso, A. R., Hauser, D. N., Bittencourt, J. C., & Correa, R. G. (2019). Dopamine: functions, signaling, and association with neurological diseases. Cellular and molecular neurobiology, 39(1), 31-59.

69. Kim, S. W., Stewart, R., Park, W. Y., Jhon, M., Lee, J. Y., Kim, S.

Y., & Yoon, J. S. (2018). Latent iron deficiency as a marker of negative symptoms in patients with first-episode schizophrenia spectrum disorder. Nutrients, 10(11), 1707.

70. Rasool, T. A., & Diab, B. S. (2022). The effect of sweet and salty taste sensitivity on gin-gival health in relation to salivary serotonin among type1 diabetic patients aged 12-14 years. Journal of Baghdad College of Dentistry, 34(3), 17-25.

71. Alajeeli, F. (2020). The Effects of Akkermansia Munciniphila on Serotonin and Fetuin-A Hormone Levels and Some Biometric Parameters in Obese Patients. Iraqi Journal of Science, 3172-3178.

72. Berthou, C., Iliou, J. P., & Barba, D. (2022). Iron, neuro-bioavailability and depression. EJHaem, 3(1), 263-275.

73. Lozoff, B., Beard, J., Connor, J., Felt, B., Georgieff, M., & Schallert, T. (2006). Long-lasting neural and behavioral effects of iron deficiency in infancy. Nutrition reviews, 64(suppl_2), S34-S43.

74. Zeidan, M. (2013). Factors associated with anemia in a sample of pregnant women attending primary health centers. Iraqi National Journal of Nursing Specialties, 26(3).

75. Haider, H. (2010). Iron Deficiency Anaemia and Beta Thalassaemia Trait in Anaemic Pregnant Women. Journal of the Faculty of Medicine Baghdad, 52(3), 282-285.