Review

The Role of Serotoninomics in Neuropsychiatric Diseases: Anthranilic Acid in Schizophrenia

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Posted Date: 20 February 2025

doi: 10.20944/preprints202502.1578.v1

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The Role of Serotoninomics in Neuropsychiatric Diseases: Anthranilic Acid in Schizophrenia

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Abstract: Serotoninomics is an expanding field that focuses on the comprehensive study of the serotoninergic system, including serotonin's biosynthesis, metabolism, and regulation, as well as related scientific methodologies (5-HT). This field explores serotonin's intricate roles in various physiological and pathological contexts. The essential amino acid tryptophan (Trp) is a precursor for several metabolic and catabolic pathways, with the kynurenine (KYN) pathway being particularly significant, representing about 95% of Trp metabolism. In contrast, only a small portion (1%-2%) of dietary Trp enters the serotonin pathway. Anthranilic acid (AA), a metabolite in the KYN pathway, has emerged as a potential biomarker and therapeutic target for schizophrenia. Elevated serum AA levels in patients with schizophrenia have been associated with neurotoxic effects and disruptions in neurotransmission, suggesting a critical role of AA in the disease's pathophysiology. Furthermore, the involvement of the 5-HT_{2A} receptor is particularly noteworthy, especially in the paranoid subtype of schizophrenia. Recent findings indicate that hyperactivity of the 5-HT_{2A} receptor is linked to positive symptoms of schizophrenia, such as hallucinations and delusions. This study investigates serotoninomics' implications for neuropsychiatric diseases, focusing on AA in schizophrenia and analysing recent research on serotonin signalling pathways and AA's neurochemical effects. Understanding the roles of the 5-HT_{2A} receptor and AA in neuropsychiatric disorders could lead to the development of more precise and less invasive diagnostic tools, specific therapeutic strategies, and improved clinical outcomes. Ongoing research is essential to uncover the exact mechanisms and therapeutic potential of these pathways, thereby advancing personalised medicine and innovative treatments in neuropsychiatry.

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1. Introduction

In this era of omics sciences, our group aims to position serotoninomics as an emerging field that focuses on the comprehensive study of the serotonergic system. This includes the biosynthesis, metabolism, transcription mechanisms, regulation, and function of serotonin or 5-hydroxytryptamine (5-HT; $C_{10}H_{12}N_2O$) in various physiological and pathological contexts. It also encompasses the technical aspects and scientific methodologies for studying the serotonin molecule [1,2]. The main methodologies that have been used or adapted as study tools for the field of serotonin in recent years include various advanced techniques such as mass spectrometry, high-performance liquid chromatography, and next-generation sequencing. Combining these strategies with emerging

 doi:10.20944/preprints202502.1578.v1

technologies supported by the advancements in laboratory instruments will lead to a better understanding of the serotonergic system's different roles across a broad range of biological systems, including neuropsychiatric diseases (see Table 1, taken from Jiménez-Trejo et al., 2023).

Table 1. Methodologies that have been used or adapted as study tools for the field of serotonin in past years and in the present.

(1) Histochemistry for indolamines or Falck-Hillarp method
(2) Brightfield immunocytochemistry and immunohistochemistry or direct or indirect immunofluorescence, single or multiplex
(3) Brightfield and fluorescence in situ hybridization
(4) Super resolution microscopy
(5) Electron microscopy and cryoelectron microscopy
(6) Fluorescence spectroscopy
(7) Flow cytometry
(8) PCR and RT-PCR
(9) Molecular genotyping
(10) Enzyme-linked immunosorbent assay (ELISA)
(11) Optogenetics
(12) Transgenic models
(13) Behavioral trials (using transgenic models, agonists and/or antagonists or other molecules acting over serotonergic pathway elements)
(14) Cell culture and 3D printed models
(15) Chromatography
(16) Western blotting
(17) 2D-gel electrophoresis
(18) CRISPR gene editing
(19) Sanger or high-performance sequencing
(20) Single-cell transcriptomic profiling
(21) Bulk-tissue RNA sequencing and single-cell RNA sequencing
(22) Electrophysiology
(23) X-ray crystallography
(24) Mass spectrometry
(25) Drug delivery via nanoparticles
(26) Genomic analysis
(27) Meta-analysis
(28) Bioinformatics

This table overviews the methodologies employed in serotonin research over the years. It encompasses a variety of tools and techniques used to investigate serotonin's role in various neuropsychiatric disorders, including schizophrenia. The table highlights these methodologies' evolution from traditional approaches to cutting-edge technologies, illustrating the progress made in the field of serotoninomics. Each listed method has contributed to our current understanding of serotonin's complex interactions and their implications for mental health.

We coined the term "serotoninomics" in 2015 [1], and since then, there has been growing interest in exploring its implications in various fields of biological sciences, including male reproduction, neuroscience, and neuropsychiatric diseases. As a whole, this will contribute to finding precise answers regarding basic, clinical, and translational research related to serotonin, just as the emerging medical and "omics" sciences have done before [3].

Additionally, it involves adapting and positioning new terms and concepts that arise in the world of serotonin with the help of the International Society for Serotonin Research (ISSR; formerly Serotonin Club) to standardise and disseminate this concept related to this indolamine [2]. The

 doi:10.20944/preprints202502.1578.v1

analysis and study of serotonin actions at different levels of the structure and function of cells, tissues, or even complete organisms will allow us to achieve a better understanding of serotonin's role in human health and disease [4,5].

Furthermore, stronger efforts must be made to achieve molecular and pharmacological treatments that are long-lasting and lack secondary effects if we want to find a cure for neuropsychiatric disorders, such as anxiety and depression, in which the serotonergic system is implicated. Understanding how different drugs (SSRIs, agonists, antagonists, and psychedelics) participate in mental illness and addiction processes is crucial for restoring such patients' mental homeostasis. Animal models, genetically encoded serotonergic sensors, and non-invasive imaging techniques are promising approaches that will gain importance in the years to come [6,7].

As we have previously described, serotonin's involvement in biological processes is extensive, and it is evident that much research remains to be done to further expand its physiological significance and achieve a more complete understanding of its role in pathologies where its balance has been altered, such as reproductive and psychiatric diseases [3,8]. Training on recent technological innovations with the help of artificial intelligence (AI) and new applications will allow us to gain new perspectives on brain function in disease, which in turn will enable us to perform better therapeutic interventions [2,7].

Together, this new holistic approach will allow us to gain a deeper understanding of how serotonin and its components influence various physiological and brain functions and, in this case, their implications for neuropsychiatric diseases such as schizophrenia. The aim is to address neuropsychiatric disorders by developing faster and more accurate diagnostics, managing targeted therapies with better drugs without side effects, and achieving more precise clinical outcomes for all those patients who require immediate and long-term care [6,7].

Schizophrenia is a complex neuropsychiatric disorder that affects millions of people worldwide (see below). Various studies have shown that serotonergic dysfunction plays a crucial role in this disease's pathophysiology. Identifying and studying key metabolites, such as anthranilic acid (AA), can provide new insights into the underlying molecular mechanisms and open the door to more effective treatments [9].

In the 2020s, it is important to position the concept of serotoninomics and expand it to encompass new perspectives and applications [2]. Recent studies have indicated that AA, a metabolite of the amino acid tryptophan (L-Trp), could play a significant role in modulating the altered serotonergic pathways in schizophrenia (as detailed below). This approach not only opens new perspectives for basic research but also raises the possibility of developing specific biomarkers for early diagnosis and monitoring of the disease [9–11].

Integrating serotoninomics into the study of neuropsychiatric diseases could revolutionise our understanding of and therapeutic approach to disorders such as schizophrenia. It will also help contribute to other omics areas, allowing us to increase our understanding of biological processes from the molecular level to complex organisms and their brain functions, as well as the resolution of psychiatric diseases. By expanding our knowledge of serotonin, we get one step closer to improving patients' quality of life and providing more effective and personalised medical solutions.

2. Psychiatric Disorders

Mental health disorders, such as schizophrenia in its various forms, are severe illnesses that affect patients' functioning in all areas of life. Common symptoms include hallucinations, delusions, and cognitive impairments. Severe mental illnesses have a devastating impact on psychosocial functioning and relationships within the family, social, and work environments. Schizophrenia is a complex, multifaceted, and multi-aetiological early-onset debilitating disorder that affects approximately 24 million people worldwide, or between 0.34% and 0.44% of the population [12]. Moreover, individuals with schizophrenic parents or siblings have a higher risk of developing the disease due to its hereditary component (between 8% and 12%) [6,7]. Some studies conceptualise

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schizophrenia as a disease of functional "dysconnectivity" [6] or "synapse disorder" [9], affecting the serotonin quantum release machinery within the synapse during its synthesis, its interaction with its receptors, or its correlation with other neurotransmitters (i.e., dopamine, glutamate, GABA) [13,14].

Dopamine has long been considered the principal neurotransmitter involved in schizophrenia's pathophysiology, playing a critical role in many of the symptoms expressed by patients with this disorder. The dopamine hypothesis posits that hyperactivity of dopamine transmission in certain brain regions, such as the mesolimbic pathway, contributes to positive symptoms like hallucinations and delusions, while hypoactivity in the prefrontal cortex is associated with negative and cognitive symptoms, such as anhedonia and impaired executive function [14,15]. This dysregulation of dopamine pathways is believed to be a core component of the disorder, influencing various aspects of its presentation and progression [16,17]. Antipsychotic medications, which primarily target dopamine receptors, have been the mainstay of treatment for schizophrenia, aiming to alleviate positive symptoms by reducing dopaminergic activity. However, these medications often come with significant side effects and may not fully address the cognitive and negative symptoms patients experience [15,17]. Understanding the complex interplay between dopamine and other neurotransmitter systems, including serotonin, is crucial for developing more effective and comprehensive schizophrenia treatment strategies.

Although its aetiology is not fully understood, in certain forms of schizophrenia, the 5-HT$_{2A}$ receptor may be involved in alterations in serotonin signalling pathways and effects, playing a crucial role in the pathogenesis of the disease, particularly of the paranoid type. Therefore, serotoninomics could offer important information for addressing psychiatric disorders such as schizophrenia [18,19]. Moreover, physicians and the pharmaceutical industry still lack definitive curative treatments, and patients and their relatives or caregivers face repeated failures in daily life [9]. Currently, few medications significantly improve the health status of patients with schizophrenia. Some antipsychotic medications can help control symptoms such as hallucinations and delusions, but they do not always fully address the cognitive and emotional problems that patients experience. Additionally, each person may respond differently to treatments, making it challenging to find an effective solution.

3. The Role of 5-HT$_{2A}$ Receptor and Other Serotonergic Pathways in Psychiatric Disorders

The Kossatz group has significantly contributed to elucidating 5-HT$_{2A}$ receptor-mediated pathways' role in paranoid schizophrenia-like behavioural responses through a multidisciplinary approach [19]. Their methodology has integrated computational models, in vitro and in vivo experiments, and postmortem human brain studies. In the latter studies, their postmortem investigations showed increased functional activity of the 5-HT$_{2A}$ receptor in the brains of patients with schizophrenia. It is known that 5-HT$_{2A}$ receptor hyperactivity has been associated with positive symptoms, such as hallucinations and delusions, making this receptor a critical and prominent target for treating this type of schizophrenia. Moreover, Kossatz et al. demonstrated that memory deficits are regulated through the activation of the Gaq protein, whereas psychosis-related behaviours are modulated through the stimulation of the Gai1 protein.

Additionally, in paranoid-like schizophrenia, the 5-HT$_{2A}$ receptor exhibits selective functional hyperactivity in the signalling pathway involving Gi/o proteins. This hyperactivity is considered a hallmark of prohallucinogenic potential [18,19]. However, more studies on this type of receptor are needed to address this important mental disorder more comprehensively and rapidly. Researchers must seek to identify new compounds related to the serotonergic system that may be more effective and have fewer side effects than conventional antipsychotics. Current research must be directed towards finding new biomarkers related to the 5-HT$_{2A}$ receptor to identify at-risk patients and develop early treatments before the end of this decade. Altogether, these data underscore the 5-HT$_{2A}$

 doi:10.20944/preprints202502.1578.v1

receptor's importance in schizophrenia's pathology and the need to continue researching to improve the available treatments.

Beyond the 5-HT_{2A} receptor, other serotonergic receptors and enzymes have been implicated in the pathophysiology of psychiatric disorders. The 5-HT_{1A} receptor, for instance, is known to play a role in anxiety and depression. Alterations in 5-HT_{1A} receptor expression and function have been linked to these conditions, suggesting that targeting this receptor could provide therapeutic benefits. Additionally, the 5-HT_{1A} receptor has been associated with cognitive functions, and its modulation may influence memory and learning processes, which are often impaired in psychiatric disorders [20].

Enzymes involved in serotonin synthesis, such as tryptophan hydroxylase 2 (TPH2), are also critical in understanding psychiatric diseases. TPH2 is the rate-limiting enzyme in the synthesis of serotonin in the brain, and genetic variations in the TPH2 gene have been associated with altered serotonin production and an increased risk of psychiatric disorders such as major depressive disorder and bipolar disorder [21]. Studies have shown that polymorphisms in the TPH2 gene can lead to reduced enzyme activity, resulting in lower serotonin levels and contributing to the pathogenesis of these disorders.

Moreover, the interaction between serotonin and other neurotransmitter systems, such as dopamine and glutamate, is crucial in the context of psychiatric disorders. The dopaminergic system, as previously discussed, is heavily implicated in schizophrenia. However, the interplay between serotonin and dopamine can influence various aspects of the disease, including symptom severity and response to treatment. Similarly, the glutamatergic system, which involves the neurotransmitter glutamate, has been linked to cognitive deficits and negative symptoms in schizophrenia. Modulating serotonergic pathways may have downstream effects on glutamate signalling, providing a potential avenue for therapeutic intervention [13,15].

In summary, the study of serotonergic receptors, enzymes, and their interactions with other neurotransmitter systems is essential for advancing our understanding of psychiatric disorders. By exploring these pathways in greater detail, researchers can develop more effective and targeted treatments, ultimately improving the quality of life for patients suffering from these debilitating conditions.

4. The Role of Anthranilic Acid in Schizophrenia

A key component of our future serotoninomics research is exploring the range of potential implications of AA. This metabolite plays a fundamental role in the kynurenine pathway, which is closely related to serotonin metabolism. Research has suggested that an imbalance in AA levels may contribute to the neurochemical abnormalities observed in patients with schizophrenia [11,22]. Therefore, AA has recently attracted attention as both a potential biomarker and a therapeutic target for schizophrenia.

L-tryptophan (L-Trp), as an essential amino acid, enters the human body through the diet. It serves as a precursor for both serotonin and melatonin and is implicated in human neuropsychiatric conditions, including schizophrenia [23]. The metabolism of L-Trp also directs to the kynurenine (Kyn) pathway, which produces several important metabolites for the brain and the immune system, including AA [24].

Recently, the dysregulation of the tryptophan-kynurenine pathway, particularly the overproduction of quinolinic acid (KYNA), has been implicated in the pathogenesis of schizophrenia and depression. However, AA's role as another secondary metabolite of kynurenine remains less explored [24,25]. Serotonin synthesis may be altered either by the disruption of the enzyme tryptophan hydroxylase 2 (TPH2, the central isoform) and its associated pathways or by the diversion of L-Trp into the kynurenine pathway. In this pathway, L-Trp is converted into N-formylkynurenine by the enzymes tryptophan 2,3-dioxygenase (TDO) and indoleamine 2,3-dioxygenase (IDO) [24,25]. N-formylkynurenine is then rapidly transformed into kynurenine by the enzyme formamidase.

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Additionally, one pathway of kynurenine metabolism produces AA via kynureninase. Although less studied, AA regulates oxidative stress and inflammation and is suspected to be neurotoxic if it accumulates excessively in certain brain nuclei [25]. Recent studies have shown a significant increase in serum AA concentrations in patients with schizophrenia compared to control subjects. This elevation of AA could be related to the downregulation of mitochondrial enzymes and the increased formation of 3-hydroxyanthranilic acid (3-HAA), a potent generator of free radicals and glutamatergic agonists. Its accumulation in key brain nuclei that regulate behaviour can lead to neurodegenerative diseases. This accumulation is particularly problematic because it can disrupt normal neurotransmission and lead to the deterioration of cognitive and behavioural functions [25,26].

Furthermore, new schizophrenia treatments are urgently needed. AA, known to be a G protein-coupled receptor 109A (GPR109A) agonist, could activate this receptor and offer beneficial effects, such as the preservation of myelin integrity and the improvement of cognitive function. This is due to its ability to inhibit cytosolic phospholipase A2 (cPLA2), an enzyme implicated in cognitive impairment associated with schizophrenia, as it breaks down myelin. This enzyme is upregulated in individuals with schizophrenia and in people at high risk of developing psychosis. However, further studies are required to elucidate these potential benefits, given the limited clinical efficacy of current antipsychotic medications. The expression of GPR109A could represent a new endophenotype of schizophrenia particularly associated with cognitive impairment, although this requires more exhaustive evaluation [27].

The AA and kynurenine pathways are essential for tryptophan degradation and the production of metabolites that modulate mental health and the immune system. These findings suggest that AA could serve as a biological marker, or endophenotype, for a subgroup of patients with schizophrenia and offer new avenues for therapeutic intervention [11]. Understanding the exact mechanisms by which AA contributes to schizophrenia's pathophysiology will be crucial for developing targeted treatments. By identifying and modulating specific pathways involving AA and related metabolites, it may be possible to reduce symptoms and improve the quality of life of patients with this type of schizophrenia [25,27].

AA's effects on the immune system and its potential to influence neurogenesis highlight its importance in the broader context of schizophrenia research. Exploring its interactions with other neurotransmitters and identifying new biomarkers could provide a more comprehensive understanding and lead to more effective therapeutic strategies. Recent clinical and experimental studies have begun to uncover these complex roles, underscoring the need for continued investigation [10,25].

Furthermore, AA's interaction with other neurotransmitter systems, such as glutamate, is also worth exploring. Glutamate, the primary excitatory neurotransmitter in the brain, plays a crucial role in synaptic plasticity and cognitive functions. Dysregulation of the glutamatergic system has been implicated in the cognitive deficits observed in schizophrenia [13]. By examining the interplay between AA and glutamate, researchers can gain insights into potential therapeutic targets to address both the cognitive and psychotic symptoms of schizophrenia.

Finally, the kynurenine pathway's role in modulating immune responses is another critical area of investigation. Inflammatory processes have been associated with schizophrenia's pathophysiology, and AA's influence on these processes could provide new avenues for therapeutic intervention. By understanding how AA modulates inflammation and immune responses, it may be possible to develop treatments that not only target the neurochemical abnormalities but also address the underlying immune dysregulation in schizophrenia [10,11,22].

5. Perspectives

The field of serotoninomics requires a more comprehensive approach from the international community to provide valuable information on the complex interaction between serotonin and

 doi:10.20944/preprints202502.1578.v1

neuropsychiatric disorders, particularly schizophrenia. Understanding the integral role of serotonin, its receptors, and related metabolites is crucial for quickly developing specific and effective treatments for these conditions. The significant findings on the 5-HT_{2A} receptor in the pathophysiology of schizophrenia, particularly its paranoid subtype, underline the importance of multidisciplinary approaches in elucidating these mechanisms and paving the way for more refined therapeutic strategies.

Furthermore, the study of anthranilic acid as part of the kynurenine pathway reveals its potential as a biomarker and therapeutic target for schizophrenia. The imbalance in AA levels and its impact on neurochemical processes underscore the need for further research on its role and the development of specific interventions to modulate this pathway. Elevated AA concentrations have been associated with neurotoxic effects and disruptions in normal neurotransmission, highlighting the importance of maintaining AA homeostasis for cognitive and behavioural health. AA's role as an agonist of the G protein-coupled receptor 109A (GPR109A) also suggests that it could represent a new endophenotype of schizophrenia, particularly associated with cognitive impairment, requiring more exhaustive evaluation.

Ongoing research on serotonin metabolism and its broader implications for mental health demonstrates that a deeper understanding of these biochemical pathways can lead to more effective treatments and improved quality of life for patients. Future studies focusing on the modulation of serotonin receptors and related metabolites, such as AA, will be essential in advancing therapeutic options and achieving better clinical outcomes for individuals with schizophrenia.

Additionally, the integration of advanced technologies such as AI and machine learning into serotoninomics research holds promise for accelerating discoveries and enhancing the precision of therapeutic approaches. These technologies can facilitate the identification of novel biomarkers, predict treatment responses, and optimize drug development processes, ultimately contributing to the advancement of personalized medicine in psychiatry.

6. Conclusion

This comprehensive review highlights how anthranilic acid and serotoninomics can play essential roles in the treatment of schizophrenia, as well as represent a new endophenotype of the disorder, opening new avenues for research and the development of innovative therapies. By continuing to unravel the complexities of serotonin and its related pathways, researchers and clinicians may develop more precise and effective interventions, ultimately contributing to the alleviation of symptoms and the improvement of life for those affected by schizophrenia. The international scientific community's collaborative efforts, combined with the application of cutting-edge technologies, will be pivotal in achieving these goals and advancing our understanding of neuropsychiatric disorders.

Author Contributions: FJ–T: Conceptualization, Data curation, Formal analysis, Funding acquisition, Investigation, Resources, Supervision, Validation, Writing – original draft, Writing – review & editing. JLC-E and KJ–G: Data curation, Formal analysis, Investigation, Project administration, Resources, Supervision, Writing – original draft, Writing – review & editing. GC–M and TL-N: Data curation, Funding acquisition, Investigation, Supervision, Validation, Writing – original draft, Writing – review & editing.

Funding: The project was supported by grant 046/2019, obtained from Federal Resources E-022 of the Instituto Nacional de Pediatría, Laboratorio Morfología Celular y Tisular, Ciudad de México, México.

Acknowledgments: We thank Dr. Isaac González-Santoyo for her support and vision to continue with this idea. We apologize to all authors whose papers are not cited because of the limitations in the number of references.

Conflicts of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

 doi:10.20944/preprints202502.1578.v1

Abbreviations

AA	Anthranilic acid
L–Trp	L–tryptophan
KYNA	kynurenine (Kyn) pathway; quinolinic acid
TPH2	tryptophan hydroxylase–2
TDO	enzyme tryptophan 2,3-dioxygenase
IDO	enzyme indoleamine 2,3-dioxygenase
3-HAA	3-hydroxyanthranilic acid
GPR109A agonist	G protein-coupled receptor 109A
cPLA2	cytosolic phospholipase A2

References

1. Jiménez, F.; Rodríguez, M. Exploring the Frontiers of Serotoninomics in Male Reproduction: The Future Ahead. *Single Cell Biol.* **2015**, *4*, 3.
2. Jiménez-Trejo, F.; Tapia-Rodríguez, M.; Arriaga-Canon, C.; Herrera, L. A.; Contreras-Espinosa, L.; Jiménez-García, K. L. Expanding the Concept of Serotoninomics: Perspectives for Serotonin Studies in the 20's of the 21st Century. *Front. Neurosci.* **2023**, *17*, 1200370.
3. Barh, D.; Zambare, A.; Azevedo, V. *OMICS: Applications in Biomedical, Agricultural, and Environmental Sciences*; CRC Press/Taylor & Francis Group: Boca Raton, FL, USA, **2013**.
4. Gaspar, P.; Cases, O.; Maroteaux, L. The Developmental Role of Serotonin: News from Mouse Molecular Genetics. *Nat. Rev. Neurosci.* **2003**, *4*, 1002–1012. doi: 10.1038/nrn1256.
5. Mohammad-Zadeh, L. F.; Moses, L.; Gwaltney-Brant, S. M. Serotonin: A Review. *J. Vet. Pharmacol. Ther.* **2008**, *31*, 187–199. doi: 10.1111/j.1365-2885.2008.00944.x.
6. Jiménez-Trejo, F.; Jiménez-García, K. L.; Canul-Medina, G. Serotonin and Schizophrenia: What Influences What? *Front. Psychiatry* **2024**, *15*, 1451248. doi: 10.3389/fpsyt.2024.1451248.
7. Jiménez-Trejo, F.; Canul-Medina, G.; López-Pech, G. Global Research in Schizophrenia and Serotonin: A Bibliometric Analysis. *Front. Psychiatry* **2024**, *14*, 1436906. doi: 10.3389/fpsyt.2023.1436906.
8. Horgan, R. P.; Kenny, L. C. 'Omic' Technologies: Genomics, Transcriptomics, Proteomics, and Metabolomics. *Obstet. Gynaecol.* **2011**, *13*, 189–195. doi: 10.1576/toag.13.3.189.27672.
9. Muneer, A. Kynurenine Pathway of Tryptophan Metabolism in Neuropsychiatric Disorders: Pathophysiologic and Therapeutic Considerations. *Clin. Psychopharmacol. Neurosci.* **2020**, *18*, 507–526.
10. Moffett, J. R.; Namboodiri, M. A. Tryptophan and the Immune Response. *Immunol. Cell Biol.* **2003**, *81*, 247–265.
11. Kuuskmäe, C.; Philips, M. A.; Kilk, K.; Haring, L.; Kangro, R.; Seppo, I.; Zilmer, M.; Vasar, E. Kynurenine Pathway Dynamics in Patients with Schizophrenia Spectrum Disorders Across the Disease Trajectory. *Psychiatry Res.* **2023**, *328*, 115423. doi: 10.1016/j.psychres.2023.115423.
12. WHO. Schizophrenia. **2022**, https://www.who.int/news-room/fact-sheets/detail/schizophrenia (accessed on 1 January 2023).
13. Moghaddam, B.; Javitt, D. From Revolution to Evolution: The Glutamate Hypothesis of Schizophrenia and Its Implication for Treatment. *Neuropsychopharmacology* **2012**, *37*, 4-15. doi:10.1038/npp.2011.181.
14. Deutch, A. Y.; Roth, R. H. The Determinants of Stress-Induced Activation of the Prefrontal Cortical Dopamine System. *Prog. Brain Res.* **1990**, *85*, 367-403. doi: 10.1016/S0079-6123(08)62687-6.
15. Howes, O. D.; Kapur, S. The Dopamine Hypothesis of Schizophrenia: Version III--The Final Common Pathway. *Schizophr. Bull.* **2009**, *35*, 549–562. doi:10.1093/schbul/sbp006.
16. Grace, A. A. Dysregulation of the Dopamine System in the Pathophysiology of Schizophrenia and Depression. *Nat. Rev. Neurosci.* **2016**, *17*, 524–532. doi: 10.1038/nrn.2016.57.
17. Brisch, R.; Saniotis, A.; Wolf, R.; Bielau, H.; Bernstein, H. G.; Steiner, J.; Bogerts, B.; Braun, A. K.; Jankowski, Z.; Gos, T. The Role of Dopamine in Schizophrenia from a Neurobiological and Evolutionary Perspective: Old Fashioned, but Still in Vogue. *Front. Psychiatry* **2014**, *5*, 47. doi: 10.3389/fpsyt.2014.00047.

 doi:10.20944/preprints202502.1578.v1

18. Meana, J. J.; González-Maeso, J. Serotonin 5-HT2A Receptors in Schizophrenia: Reflections on an Unfinished Story. *Eur. Neuropsychopharmacol.* **2023**, *74*, 89–91.
19. Kossatz, E.; Diez-Alarcia, R.; Gaitonde, S. A.; Ramon-Duaso, C.; Stepniewski, T. M.; Aranda-Garcia, D.; Muneta-Arrate, I.; Tepaz, E.; Saen-Oon, S.; Soliva, R.; Shahraki, A.; Moreira, D.; Brea, J.; Loza, M. I.; de la Torre, R.; Kolb, P.; Bouvier, M.; Meana, J. J.; Robledo, P.; Selent, J. G Protein-Specific Mechanisms in the Serotonin 5-HT2A Receptor Regulate Psychosis-Related Effects and Memory Deficits. *Nat. Commun.* **2024**, *15*, 4307.
20. Artigas, F. Serotonin Receptors Involved in Antidepressant Effects. *Pharmacol. Ther.* **2013**, *137*, 119-131. doi: 10.1016/j.pharmthera.2012.09.006.
21. Walther, D. J.; Bader, M. A Unique Central Tryptophan Hydroxylase Isoform. *Biochem. Pharmacol.* **2003**, *66*, 1673-1680. doi: 10.1016/S0006-2952(03)00517-5.
22. Shaw, C.; Hess, M.; Weimer, B. C. Microbial-Derived Tryptophan Metabolites and Their Role in Neurological Disease: Anthranilic Acid and Anthranilic Acid Derivatives. *Microorganisms* **2023**, *11*, 1825. doi: 10.3390/microorganisms11071825.
23. Kennedy, P. J.; Cryan, J. F.; Dinan, T. G.; Clarke, G. Kynurenine Pathway Metabolism and the Microbiota-Gut-Brain Axis. *Neuropharmacology* **2017**, *112*, 399–412.
24. Savitz, J.; Dantzer, R.; Meier, T. B.; Wurfel, B. E.; Victor, T. A.; McIntosh, S. A.; Ford, B. N.; Morris, H. M.; Bodurka, J.; Teague, T. K.; Drevets, W. C. Activation of the Kynurenine Pathway Is Associated with Striatal Volume in Major Depressive Disorder. *Psychoneuroendocrinology* **2015**, *62*, 54-58.
25. Schwarcz, R.; Stone, T. W. The Kynurenine Pathway and the Brain: Challenges, Controversies and Promises. *Neuropharmacology* **2017**, *112*, 237–247.
26. Davidson, M.; Rashidi, N.; Nurgali, K.; Apostolopoulos, V. The Role of Tryptophan Metabolites in Neuropsychiatric Disorders. *Int. J. Mol. Sci.* **2022**, *23*, 9968. doi: 10.3390/ijms23179968.
27. Oxenkrug, G.; Forester, B. Anthranilic Acid, a GPR109A Agonist, and Schizophrenia. *Int. J. Tryptophan Res.* **2024**, *17*, 1–6. DOI: 10.1177/11786469241239125.