

# Neurodegeneration in Cognitive Impairment and Mood Dis-orders for Experimental, Clinical and Translational Neuropsychiatry

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Editorial

# Neurodegeneration in Cognitive Impairment and Mood Disorders for Experimental, Clinical and Translational Neuropsychiatry

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## 1. Introduction

Neurodegeneration poses a significant challenge for the fields of neuroscience and medicine, as it is the underlying cause of the development and advancement of numerous neurodegenerative and psychiatric disorders [1–3]. It encompasses the progressive decay and loss of neurons across various levels of organization, ranging from molecular to network levels [4–7]. Onset can manifest at various life stages, ranging from early phases, as observed in neurodevelopmental disorders, to later stages, exemplified by conditions like Alzheimer's disease (AD) [8–10]. Neurodegeneration has the potential to impact cognitive, emotional, and behavioral functions, as well as the neural mechanisms associated with consciousness and attention [11–13]. Hence, comprehending the mechanisms and repercussions of neurodegeneration is imperative in order to identify risk factors, biomarkers, and therapeutic targets [14–16]. Nevertheless, the existing therapies for neurodegenerative disorders primarily address alleviate symptoms but are largely inadequate in terms of efficacy. Hence, there is a requirement for new and inventive methods, such as non-invasive brain stimulation, that can regulate neural activity and plasticity in a secure and reversible manner [17–21]. The field is rapidly evolving, with a focus on identifying new avenues of clinical research, elucidating potential mechanisms for the therapeutic effects of non-invasive brain stimulation (NIBS) and exploring the potential synergy between different stimulation protocols and pharmacological interventions [22–27].

The study of neurodegeneration in cognitive impairment and mood disorders is a vast and intricate domain that encounters numerous obstacles in comprehending, diagnosing, and treating these conditions [28–30]. Several existing obstacles include: The diverse and inconsistent nature of neurological and psychiatric disorders, posing challenges for the identification of shared mechanisms, biomarkers, and therapeutic targets across various subtypes, stages, and populations [31–35]; The absence of efficacious disease-altering treatments for the majority of neurodegenerative disorders, which restricts the available choices and results for patients and caregivers; The ethical and practical considerations associated with carrying out clinical trials and translational research in vulnerable and diverse populations, such as the elderly, children, and minority groups [36–38]; The

integration and interpretation data derived from various origins and modes, including genetics, epigenetics, proteomics, metabolomics, imaging, electrophysiology, and neuropsychology [39–47]; The development and validation of novel methods, such as NIBS, artificial intelligence, and drug repurposing, which necessitate thorough examination and assessment of their safety, effectiveness, and mechanisms [11,48–54]. Addressing these challenges requires collaborative efforts among researchers, clinicians, patients, and policymakers from various fields to enhance our understanding and improve the treatment of neurodegeneration underlying cognitive impairment and mood disorders [55–58]. This special issue focuses on the most recent advancements and hurdles in this area, examining them from experimental, clinical, and translational perspectives.

## 2. Special Issue Articles

### 2.1. *Stroke and Neuroprotection*

Stroke is a critical health issue characterized by the interruption of blood flow to the brain, leading to the death and harm of neurons. Neuroprotection is a key strategy aimed at protecting neurons from damage and preserving their survival and function [59–61]. In this special issue, three articles examined various approaches to promote neuroprotection in animal models of stroke [62–64]. An article by Cruz-Martínez Y et al. investigated the impact of symbiotic supplementation, comprising probiotics and prebiotics, on memory and neuronal survival in rats suffering from ischemic stroke [62]. This study tested the effects of a symbiotic (inulin and *Enterococcus faecium*). The symbiotic reduced inflammation, protected neurons, and improved memory in subacute phase. This suggests that symbiotics may be useful for stroke treatment and prevention.

To lower the risk of lacunar stroke, a type of stroke that affects the brain's small blood vessels, Zhang L et al. examined the viability of drug repurposing, a strategy that involves using fully approved drugs to treat different medical conditions. The authors used a two-sample Mendelian randomization analysis estimating the genetic variant-exposure and the genetic variant-outcome associations to identify which drugs can prevent lacunar stroke, a type of cerebral infarction [63]. This study found that genetic variants that mimic the effects of calcium channel blockers, statins, ezetimibe, and antisense anti-apoC3 agents can reduce the risk of the condition. The study suggests that these drugs should be repurposed for lacunar stroke prevention to promote healthier brain aging.

The third article by Baliellas et al. examined the impact of propentofylline (PROP), a xanthine derivative, on strengthening antioxidant defenses and decreasing lipid peroxidation in the brainstem of rats with gliotoxic injury, which serves as a model for neurodegeneration [64]. The authors tested the effects of PROP, a drug that reduces inflammation in brain cells in rats exposed to a toxic substance that causes oxidative damage in the brain. The study found that PROP prevented an increase in lipid peroxidation, a marker of oxidative stress, and enhanced the activity of glutathione reductase, an enzyme that recycles antioxidants, in the rat brainstem. This study concluded that PROP could protect the brain from oxidative damage and neurodegeneration. These articles offer a new and valuable understanding of the mechanisms and advantages of neuroprotection against stroke and related disorders.

### 2.2. *Cognitions in Schizophrenia (SCZ), Multiple Sclerosis (MS), and Down Syndrome (DS)*

Schizophrenia (SCZ) is a complex mental disorder that affects a range of cognitive capabilities, including memory, attention, reasoning, and language [65–67]. Treatment for this condition generally involves the use of antipsychotic medication, as well as psychotherapy and psychosocial interventions [68–70]. Nevertheless, the outcomes of these treatments can vary depending on several factors [71–73]. This special issue features three articles that explore various aspects of cognition in individuals with SCZ [74–76]. The articles explored how cognition is affected by factors such as the onset and duration of psychosis, severity of symptoms, level of dissociation, and resistance to treatment. Panov et al. examined the relationship between working memory, attention, and SCZ [74]. The study found that most patients with SCZ had problems with working memory and attention and

that these problems were worse in patients who did not respond to treatment. The study also found that working memory and attention problems were linked to disorganized behavior, duration of illness, and dissociative symptoms. The study suggests that working memory and attention could be used as indicators of SCZ progression and treatment response.

In another article, de Oliveira et al. investigated the feasibility of utilizing metallic nanoparticles present in the bloodstream as biomarkers for assessing cognitive performance. The research team explored how the blood levels of metallic nanoparticles affect the cognitive abilities of people with multiple sclerosis (MS) [75]. This study measured the blood levels of eight different metals and two cognitive tests in 21 patients with MS. The authors found that higher blood levels of iron, zinc, and total metals were associated with better cognitive performance. This study proposed that blood iron concentration could be a useful indicator of cognitive impairment in people with MS.

Furthermore, they examined the application of artificial intelligence as a means of improving the diagnosis and treatment of SCZ and related conditions. Koul et al. presented a review of Down syndrome (DS), a genetic disorder that causes intellectual and physical impairments [76]. This work discusses how artificial intelligence and machine learning can help diagnose and treat DS by analyzing various data sources. The text highlights the benefits of these technologies in understanding and improving the lives of people with DS. Overall, these articles provide novel knowledge that contributes to our understanding of the cognitive impairments and difficulties experienced by individuals with SCZ and their caregivers.

### *2.3. Depression and Antidepressants*

Major depressive disorder (MDD) is a widespread and debilitating mood disorder that impacts a substantial number of individuals globally [67,77–79]. Characterized by persistent feelings of sadness, reduced interest, diminished self-worth, and various physical and mental symptoms, it often co-occurs with other conditions, such as anxiety, chronic pain, and neurodegenerative diseases [80–83]. In this special issue, three articles explored different approaches for diagnosing and treating depression and its comorbidities [84–86]. The first article assessed the neuroprotective and swiftly acting antidepressant-like properties of 20 essential oils in mice. Tran et al. conducted a study aimed at assessing the potential of essential oils as rapid-acting antidepressants [84]. The study utilized cell and animal models to evaluate the neuroprotective, anti-inflammatory, and behavioral effects of essential oils. The results indicated that certain essential oils and their constituents, possibly operating through glutamate receptors, exhibited positive effects on these parameters. The study recommended additional research on *Atractylodes lancea* and *Chrysanthemum morifolium* essential oils.

In the second article, Cui et al. suggests that stimulated parotid saliva is a more accurate indicator of depressive disorder than unstimulated saliva. The authors conducted a study to investigate the influence of various saliva collection methods on cortisol levels, which are thought to be indicative of this emotional state [85]. The results of the study revealed that unstimulated whole-saliva cortisol was most closely related to blood cortisol levels, while stimulated parotid salivary cortisol was the most reliable predictor of the negative emotional condition. Furthermore, the study confirmed that individuals with depression had higher salivary cortisol levels compared to healthy controls, and that salivary cortisol levels demonstrated a positive correlation with the severity of the condition. The study proposed that salivary cortisol could serve as a useful non-invasive method for monitoring MDD.

In the third article, Rajkumar examines biomarkers associated with neurodegeneration in post-traumatic stress disorder (PTSD), a condition that has the potential to initiate or exacerbate depressive symptom. The author conducted a comprehensive review of the relationship between PTSD and neurodegenerative diseases, including AD and Parkinson's disease [86]. According to the review, a range of biomarkers, such as brain structure, genetics, inflammation, metabolism, and sleep, are linked to both PTSD and neurodegenerative disorders. The review also delved into the potential mechanisms and implications of these associations. The review found that PTSD may contribute to an increased risk of developing neurodegenerative diseases and recommended preventive measures.



## 2.4. Drug Repurposing and Cancer

Cancer is a diverse array of diseases that is distinguished by the uncontrolled expansion and invasion of abnormal cells into neighboring tissues [79,87–89]. The treatment of cancer often involves surgical intervention, chemotherapy, radiation therapy, and immunotherapy; however, these approaches have limitations and may produce adverse effects [90–92]. Therefore, the process of repurposing existing drugs for new applications, referred to as drug repurposing, offers a promising strategy for the development of novel and potent anticancer agents or adjuvants [58,93–95]. In this special issue, three articles were published that explored the potential of drug repurposing in the context of cancer and its associated challenges [96–98]. One article by Moura et al. assessed the anticancer properties of atorvastatin, a medication used to reduce cholesterol levels, and nitrofurantoin, an antibiotic [96]. The authors tested the efficacy of repurposed drugs on breast cancer and neuroblastoma cells to determine their effectiveness, both individually and in combination with doxorubicin. The results indicated that both drugs decreased the viability of both cell lines, and the combination of atorvastatin and nitrofurantoin was more effective in SH-SY5Y cells than in MCF-7 cells. The study underscores the potential use of these drugs in treating breast cancer and neuroblastoma.

In another study, Olasehinde et al. examined the beneficial impact of apigenin, a flavonoid present in plants, on mitigating cognitive and neurobehavioral impairment caused by chemotherapy. The authors conducted a comprehensive review of studies that investigated the effects of apigenin, a plant compound, on various aspects of memory and behavior in animal models of neurological disorders [99]. The review found that apigenin exhibited cognitive and neurobehavioral enhancing effects and modulated several molecular and biochemical pathways related to neuroprotection. However, the review also emphasized the need for further research to establish the optimal dosage and duration of apigenin treatment and to evaluate its efficacy in human subjects.

In the third article, Stojasavljević et al. investigated the correlation between mercury exposure and autism spectrum disorder, a neurodevelopmental condition that may elevate the likelihood of developing cancer [98]. The authors carried out a meta-analysis of studies that investigated mercury levels in various biological samples of children with and without autism. This study revealed that children with autism exhibited higher blood, plasma, and red blood cell mercury levels, but not in their hair and urine. The review proposed that children with autism had impaired mercury detoxification and excretion and that exposure to mercury could exacerbate their condition. Furthermore, the study recommended decreasing  $Hg^{++}$  exposure and closely monitoring  $Hg^{++}$  levels in children with autism. These articles offer new perspectives on the mechanisms and applications of repurposed drugs in cancer research and therapy.

## 3. Conclusions

This special issue showcases a series of papers that delve into the theme of neuroprotection from diverse perspectives and disciplines. These papers cover a wide range of conditions that affect the brain and nervous system, such as stroke, MS, DS, MDD, PTSD, breast cancer, and neuroblastoma. Additionally, the studies examine the potential of various agents and strategies to enhance neuroprotection, including symbiotics, drugs, essential oils, salivary cortisol, apigenin, and repurposed drugs. These studies have revealed the intricate and multifaceted mechanisms and pathways that underlie neuroprotection, including oxidative stress, inflammation, neurotransmission, neurogenesis, and epigenetics [100–103]. The papers also emphasize the importance of non-invasive and personalized approaches for monitoring and improving neuroprotection, such as blood iron concentration, artificial intelligence, and mercury levels. The application of these new techniques, advanced real-time analysis algorithms, machine learning, and physiological biomarkers may streamline the mental healthcare process, alleviating the social burden and economic pressures commonly associated with psychiatric disorders [104–106]. These papers make significant contributions to the field of neuroprotection by advancing knowledge and practice, and suggest new avenues for future research and intervention. The special issue highlights the

importance and relevance of neuroprotection in preventing and treating various neurological disorders, and promoting brain health and well-being.

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## Abbreviations

AD	Alzheimer's disease
DS	Down syndrome
MDD	major depressive disorder
MS	multiple sclerosis
NIBS	non-invasive brain stimulation
PROP	propentofylline
PTSD	post-traumatic stress disorder
SCZ	schizophrenia

## References

1. Rajkumar, R.P. Comorbid depression and anxiety: Integration of insights from attachment theory and cognitive neuroscience, and their implications for research and treatment. *Frontiers in Behavioral Neuroscience* **2022**, *16*, 1104928.
2. Husain, M. Transdiagnostic neurology: neuropsychiatric symptoms in neurodegenerative diseases. **2017**, *140*, 1535-1536.
3. Galts, C.P.; Bettio, L.E.; Jewett, D.C.; Yang, C.C.; Brocardo, P.S.; Rodrigues, A.L.S.; Thacker, J.S.; Gil-Mohapel, J. Depression in neurodegenerative diseases: Common mechanisms and current treatment options. *Neuroscience & Biobehavioral Reviews* **2019**, *102*, 56-84.
4. Nani, A.; Manuella, J.; Mancuso, L.; Liloia, D.; Costa, T.; Vercelli, A.; Duca, S.; Cauda, F. The pathoconnectivity network analysis of the insular cortex: a morphometric fingerprinting. *NeuroImage* **2021**, *225*, 117481.
5. Mancuso, L.; Cavuotti-Cabanillas, S.; Liloia, D.; Manuella, J.; Buzi, G.; Duca, S.; Cauda, F.; Costa, T. Default Mode Network spatial configuration varies across task domains. *bioRxiv* **2021**, 2021.2003.2017.435799.
6. Makhoulouf, A.T.; Drew, W.; Stubbs, J.L.; Taylor, J.J.; Liloia, D.; Grafman, J.; Silbersweig, D.; Fox, M.D.; Siddiqi, S.H. Heterogenous Patterns of Brain Atrophy in Schizophrenia Localize to A Common Brain Network. **2023**.
7. Turrini, S.; Wong, B.; Eldaief, M.; Press, D.Z.; Sinclair, D.A.; Koch, G.; Avenanti, A.; Santarnecchi, E. The multifactorial nature of healthy brain ageing: Brain changes, functional decline and protective factors. *Ageing Res Rev* **2023**, *88*, 101939, doi:10.1016/j.arr.2023.101939.
8. Du, H.; Yang, B.; Wang, H.; Zeng, Y.; Xin, J.; Li, X. The non-linear correlation between the volume of cerebral white matter lesions and incidence of bipolar disorder: A secondary analysis of data from a cross-sectional study. *Frontiers in Psychiatry* **2023**, *14*, 1149663.
9. Modgil, S.; Lahiri, D.K.; Sharma, V.L.; Anand, A. Role of early life exposure and environment on neurodegeneration: implications on brain disorders. *Translational neurodegeneration* **2014**, *3*, 1-14.
10. Hickman, R.A.; O'Shea, S.A.; Mehler, M.F.; Chung, W.K. Neurogenetic disorders across the lifespan: from aberrant development to degeneration. *Nat Rev Neurol* **2022**, *18*, 117-124, doi:10.1038/s41582-021-00595-5.

11. Buglio, D.S.; Marton, L.T.; Laurindo, L.F.; Guiguer, E.L.; Araújo, A.C.; Buchaim, R.L.; Goulart, R.d.A.; Rubira, C.J.; Barbalho, S.M. The role of resveratrol in mild cognitive impairment and Alzheimer's disease: A systematic review. *Journal of Medicinal Food* **2022**, *25*, 797-806.
12. Levenson, R.W.; Sturm, V.E.; Haase, C.M. Emotional and behavioral symptoms in neurodegenerative disease: a model for studying the neural bases of psychopathology. *Annu Rev Clin Psychol* **2014**, *10*, 581-606, doi:10.1146/annurev-clinpsy-032813-153653.
13. Cieslak, A.; Smith, E.E.; Lysack, J.; Ismail, Z. Case series of mild behavioral impairment: toward an understanding of the early stages of neurodegenerative diseases affecting behavior and cognition. *Int Psychogeriatr* **2018**, *30*, 273-280, doi:10.1017/s1041610217001855.
14. Tanaka, M.; Török, N.; Vécsei, L. Novel pharmaceutical approaches in dementia. In *NeuroPsychopharmacotherapy*; Springer: 2022; pp. 2803-2820.
15. Polyák, H.; Galla, Z.; Nánási, N.; Cseh, E.K.; Rajda, C.; Veres, G.; Spekker, E.; Szabó, Á.; Klivényi, P.; Tanaka, M. The tryptophan-kynurenine metabolic system is suppressed in cuprizone-induced model of demyelination simulating progressive multiple sclerosis. *Biomedicines* **2023**, *11*, 945.
16. Hansson, O. Biomarkers for neurodegenerative diseases. *Nat Med* **2021**, *27*, 954-963, doi:10.1038/s41591-021-01382-x.
17. Battaglia, S.; Schmidt, A.; Hassel, S.; Tanaka, M. Case reports in neuroimaging and stimulation. *Frontiers in Psychiatry* **2023**, *14*, 1264669.
18. Tanaka, M.; Diano, M.; Battaglia, S. Insights into structural and functional organization of the brain: evidence from neuroimaging and non-invasive brain stimulation techniques. *Frontiers in Psychiatry* **2023**, *14*, 1225755.
19. Turrini, S.; Bevacqua, N.; Cataneo, A.; Chiappini, E.; Fiori, F.; Battaglia, S.; Romei, V.; Avenanti, A. Neurophysiological Markers of Premotor-Motor Network Plasticity Predict Motor Performance in Young and Older Adults. *Biomedicines* **2023**, *11*, 1464.
20. Turrini, S.; Bevacqua, N.; Cataneo, A.; Chiappini, E.; Fiori, F.; Candidi, M.; Avenanti, A. Transcranial cortico-cortical paired associative stimulation (ccPAS) over ventral premotor-motor pathways enhances action performance and corticomotor excitability in young adults more than in elderly adults. *Front Aging Neurosci* **2023**, *15*, 1119508, doi:10.3389/fnagi.2023.1119508.
21. Menardi, A.; Rossi, S.; Koch, G.; Hampel, H.; Vergallo, A.; Nitsche, M.A.; Stern, Y.; Borroni, B.; Cappa, S.F.; Cotelli, M.; et al. Toward noninvasive brain stimulation 2.0 in Alzheimer's disease. *Ageing Res Rev* **2022**, *75*, 101555, doi:10.1016/j.arr.2021.101555.
22. Battaglia, S.; Di Fazio, C.; Mazzà, M.; Tamietto, M.; Avenanti, A. Targeting Human Glucocorticoid Receptors in Fear Learning: A Multiscale Integrated Approach to Study Functional Connectivity. *International Journal of Molecular Sciences* **2024**, *25*, 864.
23. Battaglia, M.R.; Di Fazio, C.; Battaglia, S. Activated tryptophan-kynurenine metabolic system in the human brain is associated with learned fear. *Frontiers in Molecular Neuroscience* **2023**, *16*, 1217090.
24. Battaglia, S.; Di Fazio, C.; Vicario, C.M.; Avenanti, A. Neuropharmacological modulation of N-methyl-D-aspartate, noradrenaline and endocannabinoid receptors in fear extinction learning: Synaptic transmission and plasticity. *International Journal of Molecular Sciences* **2023**, *24*, 5926.
25. Vila-Merkle, H.; González-Martínez, A.; Campos-Jiménez, R.; Martínez-Ricós, J.; Teruel-Martí, V.; Lloret, A.; Blasco-Serra, A.; Cervera-Ferri, A. Sex differences in amygdalohippocampal oscillations and neuronal activation in a rodent anxiety model and in response to infralimbic deep brain stimulation. *Frontiers in Behavioral Neuroscience* **2023**, *17*, 1122163.
26. Chu, P.-C.; Huang, C.-S.; Chang, P.-K.; Chen, R.-S.; Chen, K.-T.; Hsieh, T.-H.; Liu, H.-L. Weak Ultrasound Contributes to Neuromodulatory Effects in the Rat Motor Cortex. *International Journal of Molecular Sciences* **2023**, *24*, 2578.
27. Rymaszewska, J.; Wieczorek, T.; Fila-Witecka, K.; Smarzewska, K.; Weiser, A.; Piotrowski, P.; Tabakow, P. Various neuromodulation methods including Deep Brain Stimulation of the medial forebrain bundle combined with psychopharmacotherapy of treatment-resistant depression—Case report. *Frontiers in Psychiatry* **2023**, *13*, 3014.
28. Deyell, J.S.; Sripama, M.; Ying, M.; Mao, X. The Interplay between  $\alpha$ -Synuclein and Microglia in  $\alpha$ -Synucleinopathies. *International journal of molecular sciences* **2023**, *24*, 2477.
29. Granholm, A.C.; Boger, H.; Emborg, M.E. Mood, memory and movement: an age-related neurodegenerative complex? *Curr Aging Sci* **2008**, *1*, 133-139, doi:10.2174/1874609810801020133.
30. Hussain, M.; Kumar, P.; Khan, S.; Gordon, D.K.; Khan, S. Similarities between depression and neurodegenerative diseases: pathophysiology, challenges in diagnosis and treatment options. *Cureus* **2020**, *12*.
31. Battaglia, S.; Nazzi, C.; Thayer, J.F. Genetic differences associated with dopamine and serotonin release mediate fear-induced bradycardia in the human brain. *Translational Psychiatry* **2024**, *14*, 24.
32. Battaglia, S.; Nazzi, C.; Thayer, J. Heart's tale of trauma: Fear-conditioned heart rate changes in post-traumatic stress disorder. *Acta Psychiatrica Scandinavica* **2023**, 1-4.

33. Battaglia, S.; Nazzi, C.; Thayer, J. Fear-induced bradycardia in mental disorders: Foundations, current advances, future perspectives. *Neuroscience & Biobehavioral Reviews* **2023**, 105163.
34. Tanaka, M.; Szabó, Á.; Körtési, T.; Szok, D.; Tajti, J.; Vécsei, L. From CGRP to PACAP, VIP, and Beyond: Unraveling the Next Chapters in Migraine Treatment. *Cells* **2023**, *12*, 2649.
35. Tanaka, M.; Kádár, K.; Tóth, G.; Telegdy, G. Antidepressant-like effects of urocortin 3 fragments. *Brain Research Bulletin* **2011**, *84*, 414-418.
36. Tanaka, M.; Szabó, Á.; Vécsei, L.; Giménez-Llort, L. Emerging translational research in neurological and psychiatric diseases: from in vitro to in vivo models. **2023**, *24*, 15739.
37. Guralnik, J.M.; Kritchevsky, S.B. Translating research to promote healthy aging: the complementary role of longitudinal studies and clinical trials. *J Am Geriatr Soc* **2010**, *58 Suppl 2*, S337-342, doi:10.1111/j.1532-5415.2010.02938.x.
38. Winter, S.S.; Page-Reeves, J.M.; Page, K.A.; Haozous, E.; Solares, A.; Nicole Cordova, C.; Larson, R.S. Inclusion of special populations in clinical research: important considerations and guidelines. *J Clin Transl Res* **2018**, *4*, 56-69.
39. Tanaka, M.; Szabó, Á.; Vécsei, L. Preclinical modeling in depression and anxiety: Current challenges and future research directions. *Adv. Clin. Exp. Med* **2023**, *32*, 505-509.
40. Gračan, R.; Blažević, S.A.; Brižić, M.; Hranilovic, D. Beyond the Brain: Perinatal Exposure of Rats to Serotonin Enhancers Induces Long-Term Changes in the Jejunum and Liver. *Biomedicines* **2024**, *12*, 357.
41. Hakamata, Y.; Hori, H.; Mizukami, S.; Izawa, S.; Yoshida, F.; Moriguchi, Y.; Hanakawa, T.; Inoue, Y.; Tagaya, H. Blunted diurnal interleukin-6 rhythm is associated with amygdala emotional hyporeactivity and depression: a modulating role of gene-stressor interactions. *Frontiers in Psychiatry* **2023**, *14*, 1196235.
42. Kim, B.-H.; Kim, S.-H.; Han, C.; Jeong, H.-G.; Lee, M.-S.; Kim, J. Antidepressant-induced mania in panic disorder: a single-case study of clinical and functional connectivity characteristics. *Frontiers in Psychiatry* **2023**, *14*, 1205126.
43. Adamu, M.J.; Qiang, L.; Nyatega, C.O.; Younis, A.; Kawuwa, H.B.; Jabire, A.H.; Saminu, S. Unraveling the pathophysiology of schizophrenia: insights from structural magnetic resonance imaging studies. *Frontiers in Psychiatry* **2023**, *14*, 1188603.
44. Liu, M.; Xie, X.; Xie, J.; Tian, S.; Du, X.; Feng, H.; Zhang, H. Early-onset Alzheimer's disease with depression as the first symptom: a case report with literature review. *Frontiers in Psychiatry* **2023**, *14*, 1192562.
45. Nyatega, C.O.; Qiang, L.; Adamu, M.J.; Kawuwa, H.B. Gray matter, white matter and cerebrospinal fluid abnormalities in Parkinson's disease: A voxel-based morphometry study. *Frontiers in Psychiatry* **2022**, *13*, 1027907.
46. Liloia, D.; Cauda, F.; Uddin, L.Q.; Manuella, J.; Mancuso, L.; Keller, R.; Nani, A.; Costa, T. Revealing the selectivity of neuroanatomical alteration in autism spectrum disorder via reverse inference. *Biological Psychiatry: Cognitive Neuroscience and Neuroimaging* **2023**, *8*, 1075-1083.
47. Liloia, D.; Crocetta, A.; Cauda, F.; Duca, S.; Costa, T.; Manuella, J. Seeking Overlapping Neuroanatomical Alterations between Dyslexia and Attention-Deficit/Hyperactivity Disorder: A Meta-Analytic Replication Study. *Brain Sciences* **2022**, *12*, 1367.
48. Gregorio, F.; Battaglia, S. Advances in EEG-based functional connectivity approaches to the study of the central nervous system in health and disease. *Advances in Clinical and Experimental Medicine: Official Organ Wroclaw Medical University* **2023**.
49. Di Gregorio, F.; Steinhauser, M.; Maier, M.E.; Thayer, J.F.; Battaglia, S. Error-related cardiac deceleration: functional interplay between error-related brain activity and autonomic nervous system in performance monitoring. *Neuroscience & Biobehavioral Reviews* **2024**, 105542.
50. Ippolito, G.; Bertaccini, R.; Tarasi, L.; Di Gregorio, F.; Trajkovic, J.; Battaglia, S.; Romei, V. The role of alpha oscillations among the main neuropsychiatric disorders in the adult and developing human brain: Evidence from the last 10 years of research. *Biomedicines* **2022**, *10*, 3189.
51. Tajti, J.; Szok, D.; Csáti, A.; Szabó, Á.; Tanaka, M.; Vécsei, L. Exploring novel therapeutic targets in the common pathogenic factors in migraine and neuropathic pain. *International Journal of Molecular Sciences* **2023**, *24*, 4114.
52. Tanaka, M.; Schally, A.; Telegdy, G. Neurotransmission of the antidepressant-like effects of the growth hormone-releasing hormone antagonist MZ-4-71. *Behavioural brain research* **2012**, *228*, 388-391.
53. Tanaka, M.; Szabó, Á.; Vécsei, L. Integrating armchair, bench, and bedside research for behavioral neurology and neuropsychiatry. **2022**, *10*, 2999.
54. Vasiliu, O. Efficacy, Tolerability, and Safety of Toludesvenlafaxine for the Treatment of Major Depressive Disorder—A Narrative Review. *Pharmaceuticals* **2023**, *16*, 411.
55. Bosso, H.; Barbalho, S.M.; de Alvares Goulart, R.; Otoboni, A.M.M.B. Green coffee: economic relevance and a systematic review of the effects on human health. *Critical Reviews in Food Science and Nutrition* **2023**, *63*, 394-410.
56. Laurindo, L.F.; Barbalho, S.M.; Araújo, A.C.; Guiguer, E.L.; Mondal, A.; Bachtel, G.; Bishayee, A. Açai (Euterpe oleracea Mart.) in health and disease: A critical review. *Nutrients* **2023**, *15*, 989.



57. Barbalho, S.M.; Direito, R.; Laurindo, L.F.; Marton, L.T.; Guiguer, E.L.; Goulart, R.d.A.; Tofano, R.J.; Carvalho, A.C.; Flato, U.A.P.; Capelluppi Tofano, V.A. Ginkgo biloba in the aging process: A narrative review. *Antioxidants* **2022**, *11*, 525.
58. de Oliveira Zanuso, B.; Dos Santos, A.R.d.O.; Miola, V.F.B.; Campos, L.M.G.; Spilla, C.S.G.; Barbalho, S.M. Panax ginseng and aging related disorders: A systematic review. *Experimental Gerontology* **2022**, *161*, 111731.
59. Huang, Y.; Zhang, X.; Chen, L.; Ren, B.X.; Tang, F.R. Lycium barbarum Ameliorates Neural Damage Induced by Experimental Ischemic Stroke and Radiation Exposure. *Frontiers in Bioscience-Landmark* **2023**, *28*, 38.
60. Sarkar, S.; Raymick, J.; Imam, S. Neuroprotective and Therapeutic Strategies against Parkinson's Disease: Recent Perspectives. *Int J Mol Sci* **2016**, *17*, doi:10.3390/ijms17060904.
61. Teleanu, R.I.; Chircov, C.; Grumezescu, A.M.; Volceanov, A.; Teleanu, D.M. Antioxidant Therapies for Neuroprotection-A Review. *J Clin Med* **2019**, *8*, doi:10.3390/jcm8101659.
62. Cruz-Martínez, Y.; Aguilar-Ponce, L.; Romo-Araiza, A.; Chávez-Guerra, A.; Martiñón, S.; Ibarra-García, A.P.; Arias-Santiago, S.; Gálvez-Susano, V.; Ibarra, A. Supplementation with a Symbiotic Induced Neuroprotection and Improved Memory in Rats with Ischemic Stroke. *Biomedicines* **2024**, *12*, 209.
63. Zhang, L.; Wang, F.; Xia, K.; Yu, Z.; Fu, Y.; Huang, T.; Fan, D. Unlocking the Medicinal Mysteries: Preventing Lacunar Stroke with Drug Repurposing. *Biomedicines* **2023**, *12*, 17.
64. Baliellias, D.E.; Barros, M.P.; Vardaris, C.V.; Guariroba, M.; Poppe, S.C.; Martins, M.F.; Pereira, Á.A.; Bondan, E.F. Propentofylline Improves Thiol-Based Antioxidant Defenses and Limits Lipid Peroxidation following Gliotoxic Injury in the Rat Brainstem. *Biomedicines* **2023**, *11*, 1652.
65. Keefe, R.S.; Harvey, P.D. Cognitive impairment in schizophrenia. *Handb Exp Pharmacol* **2012**, 11-37, doi:10.1007/978-3-642-25758-2\_2.
66. Kalkstein, S.; Hurford, I.; Gur, R.C. Neurocognition in schizophrenia. *Curr Top Behav Neurosci* **2010**, *4*, 373-390, doi:10.1007/7854\_2010\_42.
67. Reichenberg, A. The assessment of neuropsychological functioning in schizophrenia. *Dialogues Clin Neurosci* **2010**, *12*, 383-392, doi:10.31887/DCNS.2010.12.3/reichenberg.
68. Ventriglio, A.; Ricci, F.; Magnifico, G.; Chumakov, E.; Torales, J.; Watson, C.; Castaldelli-Maia, J.M.; Petito, A.; Bellomo, A. Psychosocial interventions in schizophrenia: Focus on guidelines. *Int J Soc Psychiatry* **2020**, *66*, 735-747, doi:10.1177/0020764020934827.
69. De Silva, M.J.; Cooper, S.; Li, H.L.; Lund, C.; Patel, V. Effect of psychosocial interventions on social functioning in depression and schizophrenia: meta-analysis. *Br J Psychiatry* **2013**, *202*, 253-260, doi:10.1192/bjp.bp.112.118018.
70. Dickerson, F.B.; Lehman, A.F. Evidence-based psychotherapy for schizophrenia: 2011 update. *J Nerv Ment Dis* **2011**, *199*, 520-526, doi:10.1097/NMD.0b013e318225ee78.
71. Panov, G.; Panova, P. Obsessive-compulsive symptoms in patient with schizophrenia: The influence of disorganized symptoms, duration of schizophrenia, and drug resistance. *Frontiers in Psychiatry* **2023**, *14*, 1120974.
72. Lysaker, P.H.; Vohs, J.; Hillis, J.D.; Kukla, M.; Popolo, R.; Salvatore, G.; Dimaggio, G. Poor insight into schizophrenia: contributing factors, consequences and emerging treatment approaches. *Expert Rev Neurother* **2013**, *13*, 785-793, doi:10.1586/14737175.2013.811150.
73. Arnold, C.; Farhall, J.; Villagonzalo, K.A.; Sharma, K.; Thomas, N. Engagement with online psychosocial interventions for psychosis: A review and synthesis of relevant factors. *Internet Interv* **2021**, *25*, 100411, doi:10.1016/j.invent.2021.100411.
74. Panov, G.; Dyulgerova, S.; Panova, P. Cognition in Patients with Schizophrenia: Interplay between Working Memory, Disorganized Symptoms, Dissociation, and the Onset and Duration of Psychosis, as Well as Resistance to Treatment. *Biomedicines* **2023**, *11*, 3114.
75. de Oliveira, M.; Santinelli, F.B.; Lisboa-Filho, P.N.; Barbieri, F.A. The blood concentration of metallic nanoparticles is related to cognitive performance in people with multiple sclerosis: An exploratory analysis. *Biomedicines* **2023**, *11*, 1819.
76. Koul, A.M.; Ahmad, F.; Bhat, A.; Aein, Q.-u.; Ahmad, A.; Reshi, A.A.; Kaul, R.-u.-R. Unraveling Down Syndrome: From Genetic Anomaly to Artificial Intelligence-Enhanced Diagnosis. *Biomedicines* **2023**, *11*, 3284.
77. Kessler, R.C.; Berglund, P.; Demler, O.; Jin, R.; Koretz, D.; Merikangas, K.R.; Rush, A.J.; Walters, E.E.; Wang, P.S. The epidemiology of major depressive disorder: results from the National Comorbidity Survey Replication (NCS-R). *Jama* **2003**, *289*, 3095-3105, doi:10.1001/jama.289.23.3095.
78. Chamberlain, S.R.; Sahakian, B.J. The neuropsychology of mood disorders. *Curr Psychiatry Rep* **2006**, *8*, 458-463, doi:10.1007/s11920-006-0051-x.
79. Fernandes, B.S.; Hodge, J.M.; Pasco, J.A.; Berk, M.; Williams, L.J. Effects of Depression and Serotonergic Antidepressants on Bone: Mechanisms and Implications for the Treatment of Depression. *Drugs Aging* **2016**, *33*, 21-25, doi:10.1007/s40266-015-0323-4.

80. Tanaka, M.; Chen, C. Towards a mechanistic understanding of depression, anxiety, and their comorbidity: perspectives from cognitive neuroscience. *Frontiers in behavioral neuroscience* **2023**, *17*.
81. Duman, H.; Duman, H.; Puşuroğlu, M.; Yılmaz, A.S. Anxiety disorders and depression are associated with resistant hypertension. *Adv. Clin. Exp. Med* **2023**.
82. Baquero, M.; Martín, N. Depressive symptoms in neurodegenerative diseases. *World J Clin Cases* **2015**, *3*, 682-693, doi:10.12998/wjcc.v3.i8.682.
83. de Tommaso, M.; Arendt-Nielsen, L.; Defrin, R.; Kunz, M.; Pickering, G.; Valeriani, M. Pain in Neurodegenerative Disease: Current Knowledge and Future Perspectives. *Behav Neurol* **2016**, *2016*, 7576292, doi:10.1155/2016/7576292.
84. Tran, K.N.; Nguyen, N.P.K.; Nguyen, L.T.H.; Shin, H.M.; Yang, I.J. Screening for Neuroprotective and Rapid Antidepressant-like Effects of 20 Essential Oils. *Biomedicines* **2023**, *11*, doi:10.3390/biomedicines11051248.
85. Cui, Y.; Zhang, H.; Wang, S.; Lu, J.; He, J.; Liu, L.; Liu, W. Stimulated Parotid Saliva Is a Better Method for Depression Prediction. *Biomedicines* **2022**, *10*, doi:10.3390/biomedicines10092220.
86. Rajkumar, R.P. Biomarkers of Neurodegeneration in Post-Traumatic Stress Disorder: An Integrative Review. *Biomedicines* **2023**, *11*, doi:10.3390/biomedicines11051465.
87. Jinka, R.; Kapoor, R.; Sistla, P.G.; Raj, T.A.; Pande, G. Alterations in Cell-Extracellular Matrix Interactions during Progression of Cancers. *Int J Cell Biol* **2012**, *2012*, 219196, doi:10.1155/2012/219196.
88. Mierke, C.T. The fundamental role of mechanical properties in the progression of cancer disease and inflammation. *Rep Prog Phys* **2014**, *77*, 076602, doi:10.1088/0034-4885/77/7/076602.
89. Brown, J.S.; Amend, S.R.; Austin, R.H.; Gatenby, R.A.; Hammarlund, E.U.; Pienta, K.J. Updating the Definition of Cancer. *Mol Cancer Res* **2023**, *21*, 1142-1147, doi:10.1158/1541-7786.Mcr-23-0411.
90. Wargo, J.A.; Reuben, A.; Cooper, Z.A.; Oh, K.S.; Sullivan, R.J. Immune Effects of Chemotherapy, Radiation, and Targeted Therapy and Opportunities for Combination With Immunotherapy. *Semin Oncol* **2015**, *42*, 601-616, doi:10.1053/j.seminoncol.2015.05.007.
91. Colaco, R.J.; Martin, P.; Kluger, H.M.; Yu, J.B.; Chiang, V.L. Does immunotherapy increase the rate of radiation necrosis after radiosurgical treatment of brain metastases? *J Neurosurg* **2016**, *125*, 17-23, doi:10.3171/2015.6.Jns142763.
92. O'Donnell, J.S.; Hoefsmit, E.P.; Smyth, M.J.; Blank, C.U.; Teng, M.W.L. The Promise of Neoadjuvant Immunotherapy and Surgery for Cancer Treatment. *Clin Cancer Res* **2019**, *25*, 5743-5751, doi:10.1158/1078-0432.Ccr-18-2641.
93. Moura, C.; Correia, A.S.; Pereira, M.; Ribeiro, E.; Santos, J.; Vale, N. Atorvastatin and Nitrofurantoin repurposed in the context of breast cancer and neuroblastoma cells. *Biomedicines* **2023**, *11*, 903.
94. Augustin, Y.; Staines, H.M.; Krishna, S. Artemisinins as a novel anti-cancer therapy: Targeting a global cancer pandemic through drug repurposing. *Pharmacol Ther* **2020**, *216*, 107706, doi:10.1016/j.pharmthera.2020.107706.
95. Ferreira, P.M.P.; Ferreira, J.R.O.; de Sousa, R.W.R.; Bezerra, D.P.; Militão, G.C.G. Aminoquinolines as Translational Models for Drug Repurposing: Anticancer Adjuvant Properties and Toxicokinetic-Related Features. *J Oncol* **2021**, *2021*, 3569349, doi:10.1155/2021/3569349.
96. Moura, C.; Correia, A.S.; Pereira, M.; Ribeiro, E.; Santos, J.; Vale, N. Atorvastatin and Nitrofurantoin Repurposed in the Context of Breast Cancer and Neuroblastoma Cells. *Biomedicines* **2023**, *11*, doi:10.3390/biomedicines11030903.
97. Olasehinde, T.A.; Olaokun, O.O. The Beneficial Role of Apigenin against Cognitive and Neurobehavioural Dysfunction: A Systematic Review of Preclinical Investigations. *Biomedicines* **2024**, *12*, 178.
98. Stojavljević, A.; Lakićević, N.; Pavlović, S. Mercury and Autism Spectrum Disorder: Exploring the Link through Comprehensive Review and Meta-Analysis. *Biomedicines* **2023**, *11*, doi:10.3390/biomedicines11123344.
99. Olasehinde, T.A.; Olaokun, O.O. The Beneficial Role of Apigenin against Cognitive and Neurobehavioural Dysfunction: A Systematic Review of Preclinical Investigations. *Biomedicines* **2024**, *12*, doi:10.3390/biomedicines12010178.
100. Török, N.; Török, R.; Molnár, K.; Szolnoki, Z.; Somogyvári, F.; Boda, K.; Tanaka, M.; Klivényi, P.; Vécsei, L. Single Nucleotide Polymorphisms of Indoleamine 2, 3-Dioxygenase 1 Influenced the Age Onset of Parkinson's Disease. *Frontiers in Bioscience-Landmark* **2022**, *27*.
101. Correia, A.S.; Cardoso, A.; Vale, N. Oxidative Stress in Depression: The Link with the Stress Response, Neuroinflammation, Serotonin, Neurogenesis and Synaptic Plasticity. *Antioxidants (Basel)* **2023**, *12*, doi:10.3390/antiox12020470.
102. Delgado-Morales, R.; Agís-Balboa, R.C.; Esteller, M.; Berdasco, M. Epigenetic mechanisms during ageing and neurogenesis as novel therapeutic avenues in human brain disorders. *Clin Epigenetics* **2017**, *9*, 67, doi:10.1186/s13148-017-0365-z.
103. Hwang, J.Y.; Aromolaran, K.A.; Zukin, R.S. The emerging field of epigenetics in neurodegeneration and neuroprotection. *Nat Rev Neurosci* **2017**, *18*, 347-361, doi:10.1038/nrn.2017.46.

104. Borgomaneri, S.; Battaglia, S.; Avenanti, A.; di Pellegrino, G. Don't hurt me no more: State-dependent transcranial magnetic stimulation for the treatment of specific phobia. *Journal of affective disorders* **2021**, *286*, 78-79.
105. Fan, P.; Miranda, O.; Qi, X.; Kofler, J.; Sweet, R.A.; Wang, L. Unveiling the Enigma: Exploring Risk Factors and Mechanisms for Psychotic Symptoms in Alzheimer's Disease through Electronic Medical Records with Deep Learning Models. *Pharmaceuticals* **2023**, *16*, 911.
106. Sivananthan, S.; Lee, L.; Anderson, G.; Csanyi, B.; Williams, R.; Gissen, P. Buffy coat score as a biomarker of treatment response in neuronal ceroid lipofuscinosis type 2. *Brain Sciences* **2023**, *13*, 209.

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