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Neurology & Nervous System

Fight Against Alzheimer's

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Highlights

Severe Traumatic Brain Injury

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Discovering Thoughts, Inventing Future

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Evaluating Psilocybin as a Treatment for Neuropsychiatric Symptoms in Parkinson's Disease

By Nayiri Barton

Abstract- Parkinson's Disease (PD) is a progressive neurodegenerative disorder marked by motor symptoms due to dopaminergic degeneration and non-motor symptoms such as depression, anxiety, and cognitive impairment, which significantly affect patients' quality of life. Traditional dopaminergic therapies address motor symptoms but offer limited efficacy for neuropsychiatric manifestations. Psilocybin, a serotonergic compound with strong affinity for the 5-HT2A receptor, has emerged as a promising candidate for addressing the complex symptomatology of PD, including its neuropsychiatric components. This review examines the pharmacological effects of psilocybin, particularly its ability to modulate serotonergic and dopaminergic systems, enhance neuroplasticity, and reduce neuroinflammation, offering a potential therapeutic approach for PD. While clinical research in PD remains limited, evidence from related conditions such as Major Depressive Disorder (MDD) and Substance Use Disorder (SUD) supports the notion that psilocybin could modulate both motor and non-motor symptoms in PD.

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Evaluating Psilocybin as a Treatment for Neuropsychiatric Symptoms in Parkinson's Disease

Nayiri Barton

Abstract- Parkinson's Disease (PD) is a progressive neurodegenerative disorder marked by motor symptoms due to dopaminergic degeneration and non-motor symptoms such as depression, anxiety, and cognitive impairment, which significantly affect patients' quality of life. Traditional dopaminergic therapies address motor symptoms but offer limited efficacy for neuropsychiatric manifestations. Psilocybin, a serotonergic compound with strong affinity for the 5-HT2A receptor, has emerged as a promising candidate for addressing the complex symptomatology of PD, including its neuropsychiatric components. This review examines the pharmacological effects of psilocybin, particularly its ability to modulate serotonergic and dopaminergic systems, enhance neuroplasticity, and reduce neuroinflammation, offering a potential therapeutic approach for PD. While clinical research in PD remains limited, evidence from related conditions such as Major Depressive Disorder (MDD) and Substance Use Disorder (SUD) supports the notion that psilocybin could modulate both motor and non-motor symptoms in PD. Furthermore, psilocybin's ability to induce brain network hyperconnectivity and regulate dopamine release offers mechanistic insight into its potential benefits. Despite the promising neurobiological underpinnings, ethical concerns and regulatory constraints remain barriers to widespread clinical use. Future research should prioritize disease-specific trials to explore psilocybin's therapeutic efficacy, optimal dosing, and safety profile in PD, potentially redefining the treatment landscape for this underserved population.

I. Introduction

Parkinson's disease (PD) is a progressive neurodegenerative disorder primarily characterized by both motor and debilitating non-motor symptoms, including depression, anxiety, and cognitive decline. These symptoms often appear before the onset of motor deficits and contribute significantly to reduced quality of life. While dopaminergic therapies such as levodopa remain the cornerstone of motor symptom management, they offer limited benefit for neuropsychiatric symptoms and may lead to complications with prolonged use. As the limitations of conventional therapies become more evident, interest has grown in exploring alternative approaches such as psychedelic-assisted therapy. This narrative review examines the current evidence surrounding psilocybin's neurobiological mechanisms and therapeutic potential in the context of Parkinson's disease. Psilocybin, a serotonergic compound derived from certain species of mushrooms, has shown promising effects in treating mood disorders and substance use disorders by acting on the 5-HT2A receptor. PD, MDD, and SUD all involve underlying dopaminergic dysfunction, suggesting a potential mechanistic overlap. Psilocybin's ability to modulate serotonergic activity and indirectly influence dopaminergic pathways may offer a novel strategy for addressing the complex symptom profile of PD.

II. Psilocybin: Pharmacological Overview

Psilocybin is a naturally occurring psychedelic compound found in several species of mushrooms, colloquially referred to as "magic mushrooms." After ingestion, psilocybin is rapidly converted in the body to its active form, psilocin, which acts primarily as a serotonin receptor agonist, with high affinity for the 5-HT2A receptor*. Activation of this receptor is thought to underlie the drug's characteristic effects on perception, mood, and cognition. Psilocybin's influence on neural plasticity, including increased dendritic growth and synaptogenesis, has drawn significant attention for its potential in treating psychiatric and neurodegenerative disorders. These structural changes are believed to be mediated in part through downstream signaling cascades involving brain-derived neurotrophic factor (BDNF) and the mTOR pathway, both of which play crucial roles in synaptic remodeling and neuronal resilience [2].

Pharmacokinetically, psilocin typically reaches peak plasma concentration within 1 to 2 hours after oral administration, with a terminal half-life of approximately 2 to 3 hours. Despite its relatively short half-life, the subjective effects can last 4 to 6 hours, aligning well with the temporal needs of a therapeutic session. This brief but intense window of altered consciousness allows clinicians to structure therapy sessions with predictable onset and offset, reducing risks associated with prolonged intoxication. The short duration of action, combined with the low potential for physiological

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* (although mechanisms of the 5-HT1A and 5-HT2C receptors play roles in altering perception, 5-HT2A's potential will be primarily highlighted within this review)*

dependence and a favorable safety profile in controlled settings, supports the use of psilocybin in supervised clinical environments [3].

In a double-blind study on the effects of psilocybin, participants found their experience "[had] substantial personal meaning and spiritual significance and attributed to the experience sustained positive changes in attitudes and behavior consistent with changes rated by community observers" [4]. Its ability to induce meaningful psychological experiences, when administered with appropriate therapeutic support, has made it a leading candidate in the emerging field of psychedelic-assisted therapy.

III. Neurobiological Basis

a) Pathophysiology of Parkinson's Disease

Parkinson's Disease is characterized by the progressive degeneration of dopaminergic neurons in the substantia nigra, leading to a significant reduction in dopamine levels in the striatum. This dopaminergic cell loss is the hallmark of PD, which disrupts the basal ganglia's motor control pathways, resulting in motor symptoms such as bradykinesia, tremors, and rigidity. PD, however, "not only affects dopamine systems but also includes alterations in serotonergic, cholinergic, and other neurotransmitter systems, exacerbating symptoms such as depression and cognitive dysfunction," [5]. This broader involvement of neurotransmitter systems contributes to a diverse range of both motor and non-motor symptoms, including mood disorders, sleep disturbances, and cognitive decline, all of which complicate the management of PD. Moreover, the progressive nature of the disease is compounded by mechanisms like neuroinflammation, mitochondrial dysfunction, and oxidative stress, [6]. Additionally, the aggregation of, "misfolded alpha-synuclein proteins plays a central role in the progression of Parkinson's disease, leading to neuronal death and dysfunction," [7]. These multifaceted molecular processes: dopaminergic degeneration, altered neurotransmitter systems, neuroinflammation, mitochondrial dysfunction, and alpha-synuclein aggregation, collectively contribute to the complex pathophysiology of Parkinson's disease, making it a challenging disorder to treat and manage effectively.

b) 5-HT2A Receptor in Psilocybin: Mechanism of Action

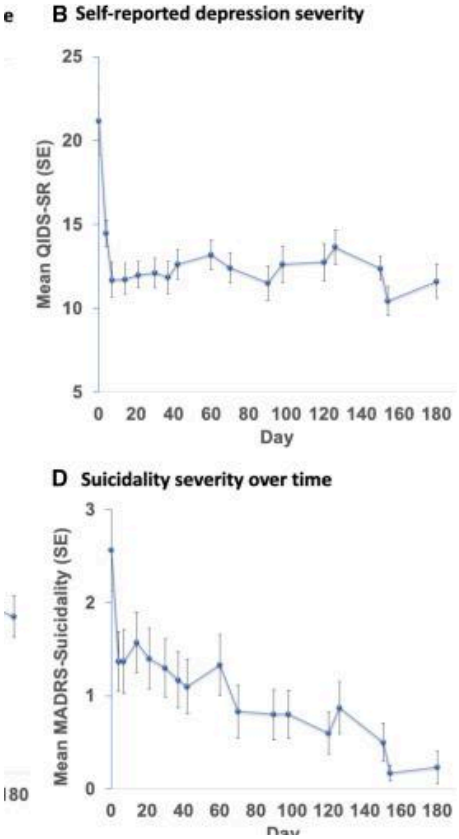
Parkinson's disease involves not only dopaminergic neuron degeneration in the substantia nigra but also early and significant changes in the serotonergic system. Degeneration of serotonergic neurons in the *raphe nuclei*, a primary source of brain serotonin, occurs early in the disease and contributes to widespread serotonin deficits. As noted, "serotonergic dysfunction is a prominent feature of Parkinson's disease, contributing significantly to both motor and nonmotor symptoms" [6]. This dysfunction underlies symptoms such as depression, anxiety, and cognitive decline. Altered serotonin receptor density and signaling, including changes in 5-HT2A receptor expression, have been observed in cortical and subcortical regions affected by PD, highlighting the critical role of serotonergic-dopaminergic interactions in the disease's pathophysiology and therapeutic approaches.

The 5-HT2A Receptor, commonly referred to as the serotonin-2A receptor, is a G-protein-coupled-receptor (GPCR) activated by the neurotransmitter serotonin (5-hydroxytryptamine). Psilocybin, a serotonergic psychedelic, exerts its primary pharmacological effects through partial agonism at the 5-HT2A receptor, densely expressed in cortical and subcortical brain regions. Activation of this receptor initiates a cascade of intracellular events, including phospholipase C stimulation and subsequent increases in intracellular calcium levels, which influence gene transcription and synaptic plasticity [7]. These signaling pathways are implicated in enhanced cortical connectivity and neuroplasticity, mechanisms increasingly viewed as therapeutically valuable in neurodegenerative diseases. Psilocybin-induced 5-HT2A receptor activation has also been shown to indirectly affect dopaminergic systems, particularly within the mesocorticolimbic and nigrostriatal pathways, suggesting a potential mechanism by which psilocybin could modulate motor and affective symptoms in Parkinson's disease, [7]. In this context, the serotonergic-dopaminergic interplay is especially relevant, as serotonin receptors may help normalize dysregulated dopamine transmission: a hallmark of PD pathophysiology. 5-HT2A activation can promote, "[mediate] Psychedelic-induced hyperconnectivity in the brain…[this] may facilitate neural rewiring, which could offer therapeutic benefits for Parkinson's disease," [9]. Collectively, these findings underscore the 5-HT2A receptor as a key mediator of psilocybin's neurophysiological effects and a potential target in the development of novel interventions for Parkinson's disease.

IV. Psilocybin in the Treatment of Neurological and Psychiatric Disorders

Historically, Psilocybin has been actively used in treating various medical and mental health conditions. Specifically focused on Substance Abuse Disorder (SUD) or addiction issues, psilocybin (specifically the properties of 5-HT2A) has been successfully proven to help mitigate symptoms of withdrawal or craving, as well as improve neuroplasticity after the effects of substance abuse damages the brain. The "proposed working mechanisms of psychedelics, including psilocybin, for improving psychiatric symptoms such as depression

and SUD are both biological (e.g., by inducing brain neuroplasticity through elevating Brain-Derived Neurotrophic Factor (BDNF) levels, which are diminished in psychiatric conditions) and psychological…," [10]. Neuroplasticity is seen in patients of addiction and neurological damage significantly after the use of Psychedelic Administration Therapy (PAP) due to psychoactive properties. Psilocybin's psychoactive properties have demonstrated clinically meaningful antidepressant effects in controlled studies. Psilocybin's favorable safety profile, particularly in controlled therapeutic settings, supports its investigational use for patients with MDD (Major Depressive Disorder). In a randomized psilocybin trial study conducted at Braxia Health in Ontario, Canada, patients (not participating in pharmacological treatment) were administered "one, two or three psilocybin sessions with a fixed dose of 25 mg synthetic psilocybin powder dissolved in water….accompanied by one preparatory therapy session (1–2 h), a supportive dosing session (6–8 h) and two integration therapy sessions (1–2 h each)...," [12]. After observing longer term effects of overall mental health, the following results can be viewed below:



[11] Psilocybin with psychological support for treatment-resistant depression: An open-label feasibility study.

Based on the mean standard errors for both depression severity and suicidality, the trial demonstrated significant reductions from baseline levels, highlighting the potential of Psilocybin therapy as a promising intervention for psychological well-being.

V. Clinical Parallels: Why Success in SUD and MDD Matters for PD

Though there has not been extensive direct research on the specific effects of psilocybin in Parkinson's disease (PD), neurobiological, mechanistic, and clinical parallels provide a biologically plausible rationale for its therapeutic exploration. Psilocybin promotes neuroplasticity by increasing dendritic spine growth and enhancing synaptic connectivity, primarily through activation of serotonin receptors such as 5-HT2A, which leads to elevated brain-derived neurotrophic factor (BDNF) levels. These neuroplastic changes have demonstrated benefits in conditions marked by impaired plasticity and neurodegeneration, including major depressive disorder (MDD) and PD [14].

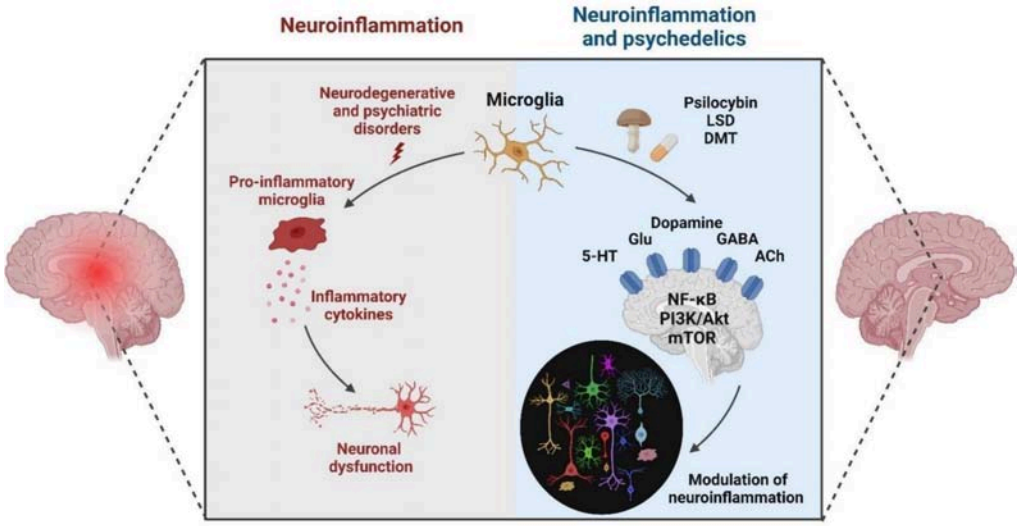
Importantly, affective symptoms such as apathy and anhedonia are shared across MDD, substance use disorder (SUD), and PD, although their clinical presentations and underlying neurocircuitry may differ. In PD, apathy often correlates with dopaminergic degeneration in nigrostriatal pathways, while in MDD and SUD, disruptions in frontostriatal and limbic circuits contribute to these symptoms. Despite these differences, all three conditions involve dysregulated reward processing and motivation pathways modulated by serotonergic and dopaminergic signaling. As reviewed, "apathy and anhedonia manifest across these

disorders through overlapping but distinct neural mechanisms, highlighting transdiagnostic relevance," [13].

Regarding BDNF, its function diverges between neurodegenerative and mood disorders. In mood disorders like MDD, reduced BDNF expression is linked primarily to impaired synaptic plasticity and neuronal resilience, contributing to mood dysregulation. In contrast, in PD, BDNF deficiency additionally exacerbates dopaminergic neuron loss and neurodegeneration. Psilocybin's ability to elevate BDNF may thus serve a dual role: restoring synaptic plasticity in mood disorders while potentially promoting neuronal survival in neurodegenerative disease [13].

Furthermore, psychedelics modulate critical intracellular signaling pathways—including nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB), phosphatidylinositol-3-kinase/protein kinase B (PI3K/Akt), and mechanistic target of rapamycin (mTOR)—that are implicated in neuroplasticity and inflammation. These pathways are disrupted across MDD, SUD, and PD, highlighting a shared therapeutic target space where psilocybin's anti-inflammatory and neurorestorative effects could have broad applicability [12].

Specific mechanism depiction can be seen below:



[12]

[12] *Augmentation in depression: Esketamine, a new standard?*

On a psychological level, a multicenter trial led by Dr. James Rucker of King's College London, found that a 25 mg dose of psilocybin on human participants, alongside psychological support, significantly impacted depression symptoms in participants with treatment-resistant depression. The study observed greater reductions in depression scores three weeks after treatment in the high-dose group compared to the placebo group [16].

VI. Current PAP and PD Conducted Research

While direct research on psilocybin's effects in Parkinson's Disease remains limited, the existing neurobiological, mechanistic, and clinical evidence suggests promising potential for its application in this population. The observed ability of psilocybin to enhance neuroplasticity, modulate inflammatory pathways, and alleviate depressive symptoms in related conditions like MDD and SUD highlights its potential as a multifaceted therapeutic approach for the non-motor symptoms of Parkinson's. A pilot study at UC San Francisco, led by Ellen R. Bradley, investigated the effects of psilocybin on mood, cognition, and motor function in individuals with Parkinson's disease. Participants experienced clinically significant improvements in mood and motor symptoms that lasted for weeks after treatment. The study suggests that psilocybin may help repair brain function and alleviate non-motor symptoms associated with PD. After administering psilocybin to a moderately sized group of participants with PD and observing results, "non-motor (MDS-UPDRS Part I: -13.8 ± 1.3, $p < 0.001$, Hedges' $g = 3.0$) and motor symptoms (Part II: -7.5 ± 0.9, $p < 0.001$, $g = 1.2$; Part III: -4.6 ± 1.3, $p = 0.001$; $g = 0.3$) as well as performance in select cognitive domains (Paired Associates Learning [-0.44 ± 0.14, $p = .003$, $g = 0.4$], Spatial Working Memory [-0.52 ± 0.17, $p = 0.003$, $g = 0.7$], and Probabilistic Reversal Learning [2.9 ± 0.9, $p = 0.003$, $g = 1.3$]) improved post-treatment," supporting the plausibility of extending findings from related conditions to PD [8]. Additionally, on a preliminary case-report done on a middle-aged woman (PD patient) with a lack of depressive-symptoms, positive effects of PAP were seen. Post-treatment, the

patient reflected on a more positive outlook on the severity of her disorder, worrying less about mortality or her future, "promoting profound decentration from habitual thoughts and emotions, improving mood and PD acceptance," [8]. Though these observed effects could be attributed to potential placebo, the existence of general outlook improvement is not one to overlook, and is often a pivotal tool for the wellbeing of those with chronic neurodegenerative disorders like PD.

VII. Neuroimaging and Mechanistic Evidence

Psilocybin has been shown to enhance brain network connectivity, particularly within the default mode network (DMN), as demonstrated by fMRI studies. These studies reveal that psilocybin induces hyperconnectivity across multiple brain regions, including the prefrontal cortex, which is associated with subjective alterations in cognition and perception, [8]. This heightened connectivity may be particularly beneficial for PD, where reduced brain connectivity contributes to both motor and non-motor symptoms, [15]. These findings support the idea that psilocybin's neuroplastic effects may provide relief from symptoms often associated with neurodegenerative conditions.

VIII. Dopamine-Serotonin System Interactions

Psilocybin's effects are mediated primarily through serotonin 5-HT2A receptor activation, which in turn influences dopamine release, particularly in regions involved in motor control. This interaction is crucial for Parkinson's Disease, where dopamine dysregulation plays a central role in both motor and non-motor symptoms. It's highlighted that psilocybin, "primarily activates serotonin 5-HT2A receptors, which modulate dopamine release, potentially alleviating symptoms related to PD" [12]. The regulation of both serotonin and dopamine systems could improve symptoms in PD patients, especially those who do not respond to conventional dopamine-based therapies, with "serotonin-dopamine interactions in Parkinson's Disease [being critical] for understanding treatment efficacy, with psilocybin potentially [modulates] both neurotransmitter systems to improve motor and non-motor symptoms" [14].

IX. Safety, Ethics, and Therapeutic Considerations

As interest in psilocybin as a therapeutic tool for neurodegenerative disorders like PD grows, safety and ethical considerations must be carefully addressed. Psilocybin, like other psychedelics, carries potential risks, particularly when used outside of controlled environments or by individuals with certain health conditions. Common side effects include transient anxiety, confusion, and disorientation, which may be particularly concerning for individuals with cognitive impairments, such as those with PD. It's not to be forgotten that psilocybin possesses psychoactive properties, with potential for hallucinogenic and psychedelic symptoms if taken at a high or non-controlled dose. However, studies have generally found that psilocybin is well-tolerated when administered in a supervised clinical setting, with careful screening to ensure patient suitability.

Additionally, the issue of cognitive decline, neural plasticity damage, and deficit as symptoms of PD become present in the ethical issue of consent by participants. Depending on the stage/onset of a participant's PD, it can potentially be a violation of conscious consent to administer a substance like psilocybin considering the patient may not be at the same level of consciousness as pre-diagnosis. In terms of decision-making, based on the pathophysiology of the disorder, "a progressive loss of cells in the midbrain producing the neurotransmitter dopamine…the controlled release of dopamine into synapses connecting the cerebral cortex and the basal ganglia plays a central role during the selection and reinforcement of actions," [10]. Due to potential decision-making impairment, the clinician in charge of administering a patient with said psychedelic must be perceptive on the patient's level of cognitive decline and ability to make a conscious decision in order to avoid ethical or HIPAA violations. Once these factors are taken into account, however, PAP appears to be an effective and low risk strategy towards cognitive and emotional recovery/stability.

X. Limitations in Current Research

Psilocybin has emerged as a leading candidate in contemporary psychedelic research. Considering this, there are still major limitations on clinical exploration/trials for neurodegenerative disorders like PD. As mentioned above, the cognitive decline and ambiguous or impaired decision-making capacity in cognitively affected individuals may raise ethical concerns regarding informed consent. Due to the severity of PD's neurodegenerative impacts, sample sizes and lengths of trials are significantly shorter than desired, therefore altering the professionalism and accuracy of results. Short trial durations and limited sample sizes restrict statistical power, increase variability, and limit the generalizability of findings. Additionally, the long-term safety profile of repeated or high-dose psilocybin administration remains insufficiently characterized, particularly for populations already vulnerable to cognitive decline or psychosis. Regulatory constraints and the classification of psilocybin as a Schedule I substance also pose

significant barriers to large-scale, multi-site studies. Until these limitations are addressed through more rigorous, targeted, and longitudinal trials (including those specific to PD), clinical recommendations for psilocybin use in neurodegenerative contexts must remain cautious and exploratory.

XI. Future Directions and Research Priorities

To fully assess psilocybin's therapeutic potential for Parkinson's Disease, future research must prioritize disease-specific clinical trials that evaluate both motor and non-motor outcomes. These studies should include larger, more diverse patient populations, with extended follow-up periods to better understand long term efficacy and safety. There is also a pressing need for trials that examine optimal dosing regimens, frequency of administration, and the role of psychological support during psychedelic-assisted therapy. Particularly, the effects of repeated dosing on serotonergic neurotoxicity, emotional lability, or precipitating latent psychosis in predisposed individuals remain poorly understood. Mechanistic studies using advanced neuroimaging and biomarker analysis, particularly those exploring serotonin-dopamine interactions and network level brain changes, will be critical in determining how psilocybin affects PD specific neurobiology. In addition, comparative trials that evaluate psilocybin against existing pharmacological and behavioral therapies could help clarify its position within the broader treatment landscape. As regulatory frameworks continue to evolve, ethical and equitable access to psychedelic therapy must remain a central concern, ensuring that any future therapeutic model is both scientifically grounded and socially responsible.

XII. Conclusion

Psilocybin emerges as a promising candidate with systematically supported potential for treating neuropsychiatric symptoms in PD. Its mechanism of action, centered on 5-HT2A receptor activation, initiates a cascade of neuroplastic and neuromodulatory processes that extend beyond mood regulation to potentially influence dopaminergic function, cortical network connectivity, and inflammatory pathways. While direct research on psilocybin in PD remains limited, strong clinical and mechanistic parallels from studies in depression and substance use disorders offer a valuable foundation for future inquiry. Although limited, early pilot data suggests that psilocybin may positively affect both motor and non motor symptoms, warranting further investigation. However, ethical, regulatory, and methodological challenges must be addressed through rigorous, disease-specific clinical trials. In particular, the use of psilocybin in vulnerable populations such as those with PD necessitates robust consent frameworks, clearly defined inclusion criteria, and stringent monitoring protocols to ensure patient safety and uphold ethical standards. Further research should prioritize Phase I safety studies in early-stage PD, with a focus on affective symptoms, quality of life metrics, and neurobiological markers of change. With appropriate safeguards and continued interdisciplinary research, psilocybin could help redefine the therapeutic landscape for Parkinson's Disease, offering a novel avenue for enhancing quality of life in a population long underserved by conventional treatments.

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Artificial Intelligence and Neural Networks with Rules based Filter are useful to Find a Correlations, between Diet and the Health Status of Multiple Sclerosis Patients, by Treating the Problem as a Surface Detector, One Can also Draw Indications on the Search for Oil and Recognize Radioactive Atoms on Neutral Surfaces

By Francesco Pia

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Keywords: food, myelinating, demyelinating, radioactivity.

GJMR-A Classification: NLMC: WL 360

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I. Introduction

Your time is precious, and we thank you for the one you will spend reading this. Since I was 7 years old I have always liked to study, and now I am the only author of the works present in the bibliography [1]-[14]. I suffer from nrsSPMS that blocks me and many patients, families, all over the world. I have opened a fundraiser on "www.gofundme.com" with the keyword "Artificial intelligence against multiple sclerosis" and thanking you, I promise that I will make every effort to ensure that the funds raised will be spent on the next works that will surely be expensive.

Author: prof. PhD Eng. Gonnosfanadiga (SU), Italy. www.gofundme.com keyword "Artificial intelligence vs Multiple Sclerosis". e-mail: piafranc@hotmail.com

In this work three applications of a versatile "intelligent" system as a "surface analyzer" will be presented, in different chapters: the first on Multiple Sclerosis, the second as a detector of oil, water or other, the third for the identification of heavy and radioactive atoms.

II. Diet and Multiple Sclerosis

In this chapter we will try to adapt the intelligent systems present in [12], [14] in order to improve the analysis capabilities and to further test the "seed of discernment" present in [12] and [14] in "surface analysis" problems. and in particular, in this chapter, in the link between the diet assumed by a newly diagnosed multiple sclerosis patient and his state of well-being by virtue of mylinizing or demylinizing foods.

In the following lines we will try to give some indications for the newly diagnosed or not that emerged from the experience of the undersigned that each reader will evaluate independently or followed by his neurologist.

1. Doing sports, fitness and any activity with your body
2. Stem cell implant, after medical opinion from different bell towers
3. Assumer TOLEMABRUTINIB® by SANOFI®, PIPE 3O7® Contineum Therapeutics, Inc. of hoping my neurologist agrees, I'm waiting anxiously.
4. Resorting to the intermittent diet.
5. Use, with the help of a nutritionist, mainly myelinizating foods.

In this chapter we address the problem of diet in "newly" diagnosed patients with multiple sclerosis, which can be myelinating or demyelinating depending on dietary intake, addressing it with artificial intelligence with an architecture based mainly on Back-Propagation neural networks.The inputs used are to be considered "pseudo cybernetic" but of natural origin that can be for or against the increase of myelin in circulation. Through the use of NNs connected with appropriate architectures, a system could be built that highlights the

reaction, in the medium-long term, of the human body to natural inputs available such as food; without machines, weight indicators, strength, and only thanks to the musculoskeletal response felt and self-assessed by the subject who adheres to this diet here simply called "*diet*".

The research of information, and data, was conducted thanks to the "volatile" WEB, a type of information that is not necessarily collected in specific sites, so there will be no bibliographic references nor authors and their works, only thanks to the various navigators that bring the data to light. It is very important to take into consideration the fact that these pages do not want to give precise, exhaustive indications on the eating habits of newly diagnosed people. In fact, some people may like some foods that are indicated as demyelinating, for example by eliminating them, and in that case they would have others, difficult to correlate with positive and demyelinating effects. Each patient, and not only, can freely interpret under his experience the indications that the system will provide him; as he could, on the contrary, feed himself with myelinating elements that give him more strength than others, not indicated or unfortunately given as demyelinating by the system; therefore, if he does not find anything to replace them, or integrate them, he will be able to interact with the system by leaving a feedback. The data used in this work are those that emerge from browser searches and displayed in summary form: this type of data is called, in this work, "volatile"; that is, high-level information, if they were low-level (such as saying that one would have the duty to eat... as in the bibliography would find...), with these data it will be a duty for the user, after entering them into the system and following the nutritionist's instructions.

So, whoever goes on a diet is considered a "natural" cybernetic system with input and programmed because the diet is still a nutritional reprogramming of the body whose outputs are deduced by the user who perceives a possible benefit or not..

Foods are either remyelinating or demyelinating. In this work, few elements are evaluated; in fact, it is a system that can be modified or expanded.

The “seed of discernment [12]” has been used in all three chapters: the use of two NNs, appropriately interconnected, which give a nuanced response, where the response is the motor improvement or not that the user can report. This scheme is present in [12] where the same type of approach is used, but in this work no laboratory tests will be performed, but reference will be made to the state of well-being reported by the user. The Sulfurin is a rare, myelinating substance that can repair myelin; the naturally occurring molecule blocks the activity of an enzyme that is overactive in areas of myelin damage. This same enzyme also contributes to the growth and spread of cancer cells, meaning the discovery has implications beyond MS. Study co-author Angela Hoffman, a professor at the University of Portland who had been examining nearly unobtainable plant-based hyaluronidase inhibitors, and Steve Bryson and colleagues at Oregon Health & Science University say it's exciting that the plant-based molecule can inhibit the growth of myelin-producing cells [14].

Our body contains about 21 mg of Potassium 40, and emits β rays and neutrinos (cosmic objects) about 400 million/day; it could also repair itself, and implement remedies with the right stimulations. In this work we use foods in two groups as stimuli: remyelinating and demyelinating, the first ones help myelination the second ones damage it. Artificial Intelligence can be useful to verify if this reasoning is coherent. We do not want to question foods that are eaten daily by those who are not diagnosed with MS; such as cereals for many people, however, certain foods that the network indicates as such are considered myelinating. The research, in this work, is also sometimes superfluous since for the simulation it would be enough to insert generic foods, for example from the Mediterranean diet; dividing them into categories: this is important because the present system is made up of two Neural Networks that use the so-called "Seed of Discernment" [12]: the first work where MS is studied with AI.

Given the paradigm: move and you will move, stay still and you will stay still: let's assume the metabolization of the food taken in the diet. This paradigm can be used as an input, with any type of diet, drug, etc. etc. without exercise it is almost all useless; that is, if you take a "new drug" and do not follow adequate physiotherapy it is almost useless. Instead, considering physical activity as a myelinating factor and staying still as a demyelinating one, it can be used as an input, in a specific APP, metabolized by movement. It would not be wrong to imagine that since a myelinating food introduced, not metabolized does not go into circulation, but is only digested; but if metabolized it is more likely to have a myelinating effect.

a) A Linear Algebra for Surface Analysis

From the following table tab.1 it is possible to extract a square matrix to obtain a function that highlights the trend of the new data, compared to the average of the previous data, from which we consider the average. The matrix can be constructed as a square by joining the rows with low quantity impact (for example dietary) and adding columns that take into account the response of the various outputs (for example parts of the patient's body subjected to the diet) and other non-linearly dependent on the previous ones, useful for describing the state of the system (for example the patient's health).

Let's proceed by making the data in array form. Given the original array $\left[Q\right]$, a random reallocation of its various cells is carried out, obtaining $\left[\overrightarrow{R}\right]$ of which we would calculate the average and normalization.

I then subtract that of the new day of the same patient $\left[\overline{G}\right]$:

$$\left[\overline{R}\right]^{1\to j} - \left[\overline{G}\right]^{j+1\to i}$$

$\left(j+1 \to i \right)$ for any days more than one; from which we can calculate:

$$(a) \quad \left[P\right] = \nabla\left(f\left(div \left[\overline{R}\right]^{1\to j} - \left[\overline{G}\right]^{j+1\to i}\right)\right) \begin{cases} > \\ = \quad 0 \\ < \end{cases} \quad {}^{*?}$$

After proper reallocation to the original cells of patient:

Gistificare la riallocazione, così che nnon vengano considerate le posizioni sempre presesnti specificare mmeglio l'analisi di superfice

$$(b) \quad \left[\overleftarrow{P}\right]$$

$$(c) \quad \begin{cases} > 0 & \text{perhaps it has a negative impact} \\ = 0 & \text{it's almost indifferent} \\ < 0 & \text{perhaps it has a positive influence} \end{cases}$$

From the examination of (c) we can use NNs to get more information, we call Nnhope a neural network with multi-layer perceptron architecture with three layers and back-propagation learning algorithm with inputs and outputs equal to the number of cells of the matrices used so far and trained "*artfully*" to recognize what are the hypotheses, for better or for worse, examined so far on the myelinating diet or not with advantages, or less, on the various musculoskeletal districts examined for each patient subject to the diet.

Using the following scheme we will have to obtain more and more detailed information on how to adjust the diet to follow:

*? The use of certain mathematical operators, matrix ones, and not others, has as its objective the obtaining of a scalar; it would probably be sufficient to use only the calculation of the determinant of the matrix which is the argument of the operator

$$\left[\overleftarrow{P}\right] \Rightarrow \boxed{\begin{array}{c}\text{Neural Network} \\ \text{Back Progation} \\ \text{NNhope}\end{array}} \Rightarrow \left[hope\right] \qquad (c)$$

From the examination of the matrix [hope] the salient data can be reported to the nutritionist and neurologist for the corrections of the case and the various conclusions. The undersigned follows, not at 100%, the indications reported in table 1 and are not detecting worsening but very slight improvements that fall within the fluctuating clinical picture of multiple sclerosis, however the results are expected in the long term. It is believed that this approach will most likely give positive and more visible results in mild forms and in newly diagnosed than in those who have been affected for years by the nrSPMS form like the undersigned who after the end of this work in addition to continuing the diet will dedicate himself more to rehabilitative physiotherapy and physical exercise.

III. Methods and Tools

This paragraph will describe the main scheme of the setup that will be used, also in the next works and the present one which mainly describes the idea, and the second one which involves the use of neural networks and the drafting of an algorithm especially by virtue of the fact that the patients will be virtually encapsulated while the third will be much more challenging because the use of "*real*" patients; at this point in the exposition it is not easy to use real patients.

In the following figures everything is particularly "simplified" because only the preliminary project that will be described is represented, represented in the figures fig. 1, 2. All this is obviously simple compared to the scale of the overall project. As said in the introduction, it is not very useful to describe in depth these blocks that are part of the drawings represented in fig. 1 and 2 because the difficulties that will be encountered will not be few and above all the methods used to describe and realize the various components will not be simple, and the type of representation and its representation is unpredictable.

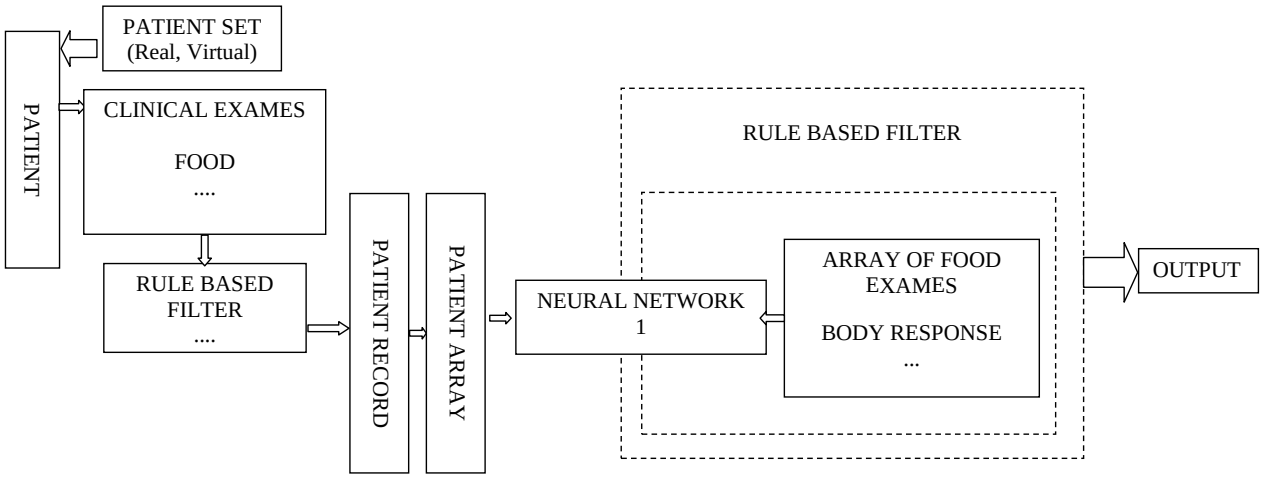


Fig. 1: This Figure Represents the Original Idea to Train A Neural Network to Distinguish an MS Patient from a Healthy One, as Well as "Memorizing" the Cases Seen in Training

Tab. 1: This Table Represents the "i-th" Patient

$Patient_i$		$Diet_i$	Response	Example of a rule indicated by the nutritionist
$Food_i$	MY/DEMY	RULES/GRAMS	$Diet_i$	
Dried fruit	My	$rule_1$	R_i	...
animal proteins	My	$rule_2$		$0 \leq 20[g]$
Fruits and vegetables	My	$rule_3$		...
Sulphuretin	My	$rule_4$		...
Fish + Ω_3	My	$rule_5$		...
Ω_3	My	$rule_6$		...
Biotin	My	$rule_7$		$0 \leq 400[mg]$
Vitamins B1, B2, B3, B5, B6, B12, C, Niacin	My	$rule_8$		...
Legumes	My	$rule_9$		...
				$\sum_{i=1}^{20} KCal_i \leq 2100[KCal]$
Grape seeds	MY/DEMY	$rule_{10}$		...
Salt	DEMY	$rule_{11}$		0
Sugar	DEMY	$rule_{12}$		0
Butter	DEMY	$rule_{13}$		...
Oil	DEMY	$rule_{14}$		
Refined foods	DEMY	$rule_{15}$		...
Beer	DEMY	$rule_{16}$		0
Dairy products	DEMY	$rule_{17}$		...
pork sausages	DEMY	$rule_{18}$		...
Cereals	DEMY	$rule_{19}$		...
Carbohydrates	DEMY	$rule_{20}$		...
$1 \leq PATIENT_i \leq 30$	2100 KCal	$rule_i$ $0 \leq KCal_i \leq g_i$	RESPONSE $0 \leq R \leq 1$	

Many foods, such as legumes "*for example*", are very healthy if present in the diet but the effects on myelin are not known, this fact we here would call the "*bean problem*"

For The patients' response is certainly subjective, but the intelligent system will most likely be able to give useful indications for MD clinicians will be used, hoping to limit the number of inputs, and since they are numerous, it will be necessary to ensure that the NN *[6], [12]* has a variable and selectable range for the inputs.

At this point in the simulation, it is recommended to use 10 patients for the system training phase, 10 for validation and 10 for testing.

At this point the first neural network should be able to associate food with the response of the sick patient at the onset of multiple sclerosis, but this is not what we would like only. In fact, thanks to the second NN, the most myelinating foods and their quantity to be taken daily should be noted with the supervision of the nutritionist and the neurologist. The following figure further highlights the potential of diet-patient matching highlighted in Figure fig. 1. The male/female ratio is an important factor for patient selection and the impact of MS, which must be represented in the patient population and therefore will be implicit in the selected sample.

As for training, validation should be done on MS patients, while for the testing phase it would be interesting to insert some patients with variable expressed parameters in the simulations: *new*, *old* and *healthy*, to try to represent the whole population. Over-fitting should be avoided by shifting the just evoked parameters and their respective inputs and by a somewhat broader representation of the output and inputs.

The following figure fig. 2 shows the system just exposed; that is, a system able to indicate significant parameters to be provided to the clinician with the totality of patients and simulated data thanks to ***Tab. 1***.

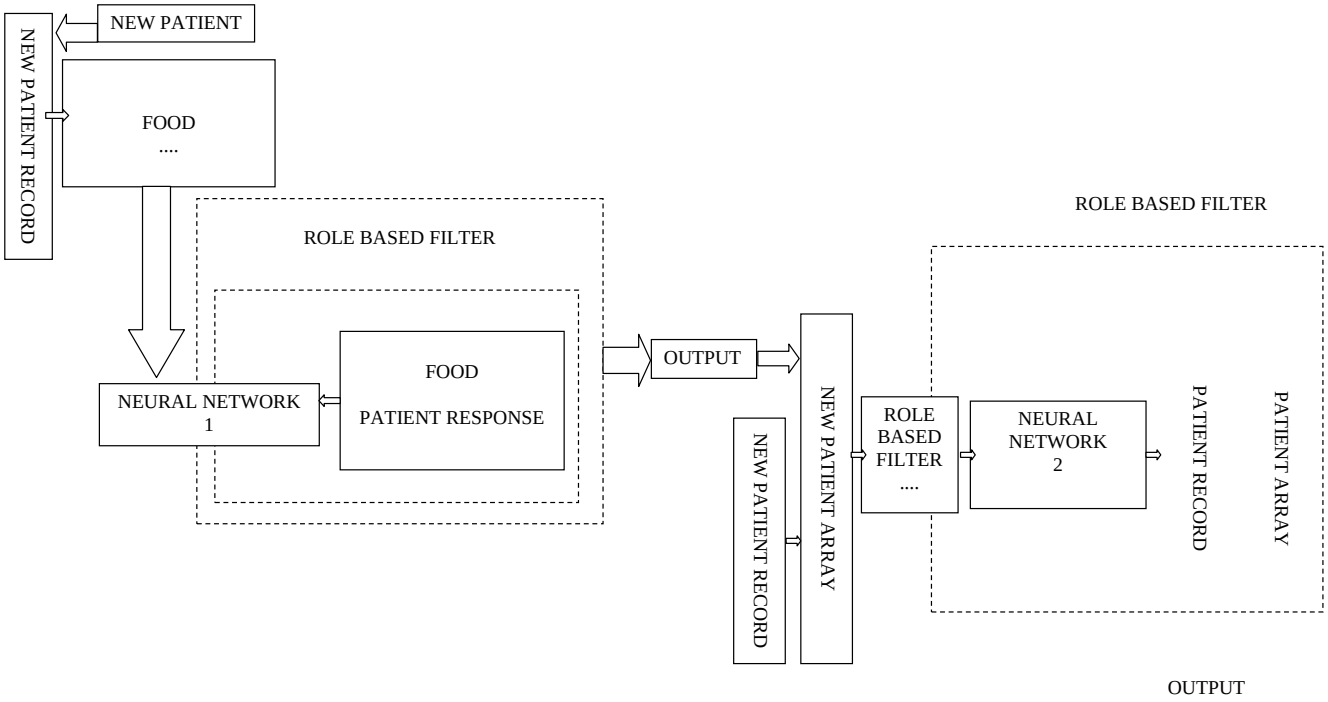
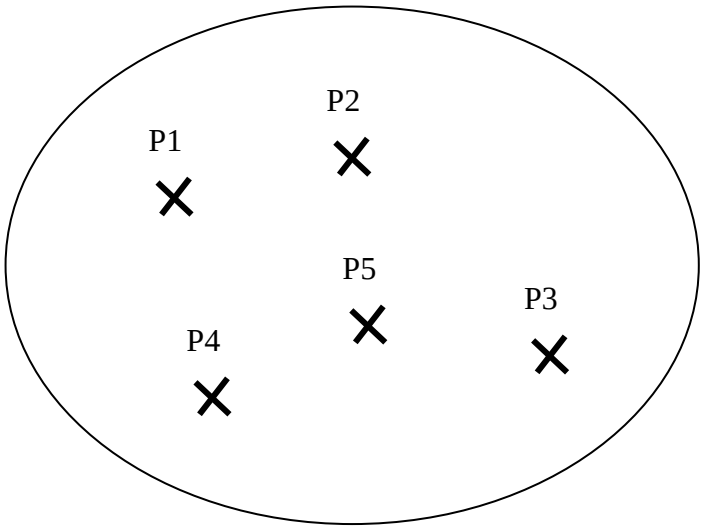


Fig. 2: This Figure Represents the Second Part of the System Which Could Give Important Indications to the DIET

To clarify, training can be done on "newly diagnosed" patients and validation on those "diagnosed not long ago" the Test is a somewhat nuanced middle ground, a bit of the first group and a bit of the second, assuming that the system in fig.1 is able to distinguish a healthy patient from a sick one by his diet, then we ask ourselves where the information resides?

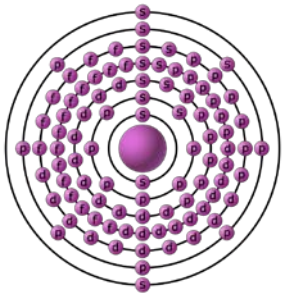
The information and the result of the correct training of the NN n°1 of the successful learning of the diet-patient pairing; and up to this point after having carried out the training: then an average of the input vectors of the arrays of the patients and their diets is made and the significant food could be hidden, in truth the input of interest appears: then a new case is presented and at this point the network will say the most mylinizating diet and the difference is made between the representative vector of the new case minus the average of the patients, then we will see what are the variables in play that determine this difference between the representative vectors. The schemes proposed in fig. 1 and 2 should be considered a common place that can also be used for other pathologies, this aspect is very important to underline.

IV. Indications on the Search for Oil



Well	Coordinates		PROFONDITA	
P1	x	y	P	
P2				
P3				
P4				
P5				
...				

V. Recognition of Radioactive Atoms on Neutral Surfaces



VI. Conclusion

Since we intend to proceed, at the end of this mainly descriptive work on the idea of using NNs, other steps are substantially planned that will concern the introduction of over-the-counter drugs into the entrances and then prescribed by the neurologist and with a lot of work to do. Once the correct functioning of the virtual encapsulator of the patient and the entire system has been verified, and the presence of sufficient funds has been verified, to then try to concretely implement the procedure that should answer, in part, the question of the title of this work, thus giving indications to clinical doctors who are experts in the sector covered in this article.

The undersigned, who has been following this diet for a month and more, has noticed great improvements, even if... due to autosuggestion. After all, due to waiting for drugs that never arrives: there's no harm in trying. Funds are needed for software simulations and the undersigned, in addition to making himself available, strongly recommends contacting competent doctors in the various fields of medicine. And like many things in the life of those affected by MS, even a diet must not deprive us of a few moments of happiness. For example, a pizza party with friends (pizza and beer): two non-myelinating foods and we do not participate, aware or not we are not happy but sad and depressed by the renunciation. Such suffering could make us lose the results obtained after months of myelinating diet: the diet should perhaps be faced with a serene, friendly spirit, like the life of a patient, and not only, of MS. We would say balance and serenity: therefore a yes with moderate behavior to pizza and beer with friends.

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An extraordinary thank you to all those who take care of people with physical and mental disabilities.
In particular at my lovely family.

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Toward a Neurocounseling Paradigm: The Science Behind Step One in Addiction Recovery

By Ashton, C. & Duffie, D.

Abstract- Facilitating successful early and sustained remission from substance use disorder remains an extraordinarily difficult puzzle for both clients and supporting persons to navigate. Ninety years since Alcoholics Anonymous developed its twelve step, spiritual approach to recovery from the devastation of alcoholism, initiating and sustaining abstinence from addictive substances remains a tremendous challenge. While the 12-step community continues to support addicted persons at no cost through meetings and relationships, psychology, counseling and medicine are continuing to develop approaches for people to achieve recovery from addiction. To date, there is minimal convergence in these approaches leaving affected individuals with often confusing choices in seeking necessary recovery support. The unfortunate result is the predominant view of substance use disorder as a chronic relapsing disorder whereby relapse is embedded as fundamental to its nature. Greater societal stressors and increasingly dangerous substance access is resulting in death by overdose becoming a major public health issue.

GJMR-A Classification: *NLM: WM 270*

Strictly as per the compliance and regulations of:

Toward a Neurocounseling Paradigm: The Science Behind Step One in Addiction Recovery

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Rapid advances in diagnostic and imaging research techniques over the past two decades, have given tremendous insights into central nervous system functioning at cellular and systems levels. Building on pioneering work in the behavioural neuroscience of addiction, this paper enriches and unifies the often-divergent approaches taken by addicted persons and loved ones, supporting professionals, and peer support groups in addiction recovery. Through a systems neurobiological approach, we outline the progressive neuroadaptations in the limbic system which lead to the condition described by Alcoholics Anonymous as powerless. Understanding the veracity of this central issue in addiction provides an approach we name as Neurocounseling, providing the opportunity for agreement and synergy across approaches. With neuroplasticity as a guiding principle both in progression of the disorder, as well as in the attainment of recovery, addiction can be more appropriately viewed as a life experience rather than a life sentence.

I. Introduction

In 1939, Alcoholics Anonymous (AA) World Services Inc. published its text which, remarkably, is still in broad use today and shows no signs of losing popularity. Within the profession of caring for people suffering from addictions of all types in residential and ambulatory care sites, the Twelve Steps still remain a gold or, at minimum, a comparison standard. On the other hand, the field of addiction counselling is emerging in response to significantly growing population needs. Addiction Counsellors have developed professional certifications and licensing through embracing well developed therapeutic modalities (CCPA, 2025) and the scientific method. For the most part, the two approaches are believed to complement each other; it is rare that any current addictions counsellor would dissuade a client from attending a free support group.

The two predominant approaches, counselling and twelve step programs differ significantly: AA clearly advocates its approach through the twelves steps as spiritual in nature (Big Book, Appendix II, 2001). Counselling and psychotherapy are the skilled and principled use of relationship to facilitate self-knowledge, emotional acceptance and growth and the optimal development of personal resources (CCPA, 2025). Counseling modalities have embraced the scientific method for both developing and assessing the effectiveness of its various modalities (Fordham, B. et al, 2021). However, robust long term outcomes studies have not yet taken place whichclearly identify evidence for best approachesfor addressing addiction since Project Match (*Project Match Research Group*, 1998).

Project Match was a multi-centre study conducted from 1989 to 1997 which has received considerable criticism of its methods in the scientific field (Walters, G., 2002). Regardless, it failed to show any significant difference among any counselling methods and 12 Step programs in outcomes: most enrolled alcoholics showed minimal change in their drinking patterns at the one-year point. Studies since in the areas of treatment outcomes for addictions have been significantly smaller in terms of participants and time length. Our own commissioned work of 2014 (Ashton, C. and Duffie, D., 2014) exploring potential best practices in residential treatment for addictions revealed very few articles, and those centres that did publish reliable outcomes showed a success rate around 20% overall at one year for clients.

In the absence of clear directions for counseling best practices and a multitude of potential options, the treatment industry has currently defaulted to a position which now assumes that each person finds their own path into recovery. Choice of types of therapy is mainly at the client's direction and consensus with the counsellor. There has, however, been a potentially paradigm-shifting body of knowledge which has emanated from advanced brain imaging techniques (PET and functional magnetic resonance imaging (fMRI)) and microbiology research technologies over the

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past 20 years. What can be collectively termed the neuroscience of addiction has provided incredible insights into relatively uniform and consistent pathways of addiction in the limbic system of the brain. That being said, wehave yet seen little of the potential of neuroscience incorporated into present day programs (Verdejo-Garcia, A., 2019).

Our experience in treatment has strongly indicated that those persons who do achieve sustained recovery attribute their success to one predominant ideology that leaves the other far secondary in terms of perceived impact. This may be a suboptimal outcome in many cases. We have developed a novel and extraordinarily successful methodology to addiction counselling whereby the two philosophies merge through the neuroscience of addiction. Counseling and educating clients in the neuroscience behind Step One of AA is an approach that clients find fascinating and immensely gratifying through finally understanding the reasons for the complex array of compulsive and self-destructive thoughts, emotions and behaviours in addiction. Effective in facilitating sustained remission for 83% of clients who complete the 30-day program, understanding the science of recovery through progressive, healthy neuroadaptations allows anticipation of challenges and accelerates the process toward healthy, neurotypical function.

The fields of psychology, addiction medicine and addiction counselling continue to make strides through research and practice. Counselling modalities such as cognitive behavioural therapy (CBT), dialectical behavioural therapy (DBT), motivational interviewing (MI) and acceptance commitment therapy (ACT) have become more refined, formalized and have a growing literature base. Their specific application at the varying stages of change (Prochaska and DiClemente, 1983) has become better articulated.

Drawing on the extraordinary work published in the field, our Step One method uses a robust neuroscientificevidence base to unify current counseling modalities with AA's first step to develop a common, highly effective framework.Coming to terms with the detailed organicism of addiction allows a tangible comprehension of the seeming incorporeal influence of substances over affected persons. At the same time, our program stimulates broader existential questions in contemplating the complexity and terrible perfection of this disorder, merging with the spiritual approach of AA.

a) Introduction to Applied Behavioural Neuroscience

Our development of Step One Therapy began with a consideration of AA's Step 1:

> "We admitted we were powerless over alcohol— that our lives had become unmanageable."

A difficult admission for people faces even more resistance when the basis for recovery according to the Big Book is dependence on higher power and a spiritual solution. While it still gains favour among many, an abstract solution to excruciatingly painful, tangible human issues often gathers only minor commitment and unfortunately does not work for the vast majority of persons who try the program (*Project Match Research Group,* 1998). On the other hand, the counselling profession, as advanced as it is becoming, has yet to produce robust evidence of better efficacy with addictionsthan twelve step methods since Project Match. Current systematic reviews (Balandeh et al, 2021) of CBT applied to addictions treatment still refer to it as a 'promising practice.' Since Project Match, a thorough review of the literature still shows a paucity of studies whereby adding the two therapies may prove summative.

Years of attending AA and Narcotics Anonymous and listening to people's narratives convinced us that the first half of Step 1, 'we admitted we were powerless,' was true. Since the AA text represented the only means of communicating to a potentially mass audience about this new solution for alcoholism in 1939, it was very carefully written. The Oxford English Dictionary of that era defines powerless as: 'without power or ability; devoid of power, helpless.' AA explains this as losing 'the power to choose whether he will drink or not.' The AA text expands on this state throughout the text speaking of the 'peculiar mental twist already acquired' whereby alcohol always wins out over willpower. Importantly, writing two years after AA formed, the text speaks to its members as 'were powerless,' indicating they had recovered (Alcoholics Anonymous, 1939).

The second part of Step 1, 'that our lives had become unmanageable,' is consistently given witness by the narratives of the varying terrible life circumstances that one comes into recovery with. Our notion in this regard was that this was attributable to more complexity than simply the cost of alcohol or behaviour when highly intoxicated on drugs or alcohol. Rather, when combined with the first half of Step 1, we surmised that the reason behind powerlessness and unmanageable life circumstances was fundamentally a broader disorder of decision making, preceding and progressive with the development of addiction.

Our framework builds on established models, in particular the iRISA (impaired Response Inhibition and Salience Attribution) (Goldstein, R. and Volkow, N., 2001; Kwako, L. et al, 2016; Ceceli, A. et al, 2023) modelwhere the neurobiology of salience of drug cues is postulated to overpower that of other reinforcers with a concomitant decrease in self-control. The iRISA model underpins the familiar cycle in addiction as shown in Figure 1 below:

(Goldstein, R. and Volkow, N., 2001)

Figure 1: Behavioral Manifestations of the I-RISA (Impaired Response Inhibition and Salience Attribution) Syndrome of Drug Addiction

In further exploring the neurobiology or Step One, we additionally postulated that the severe dysphoria, often encountered in withdrawal, had a neurobiological basis which contributed to the overpowering of inhibitory circuitry demonstrated in the prefrontal cortex (Ceceli, A. et al, 2023). Contemplating the seemingly inexplicable relapses in persons in early recovery just as positive life changes seemed to be occurring, our exploration in this regard was guided by previous work on the anti-reward system in addiction (Koob, G. and Le Moal, M., 2008). The anti-reward system refers to behavioural processes, such as aversion and avoidance, that are part of the normal homeostasis in reward function.

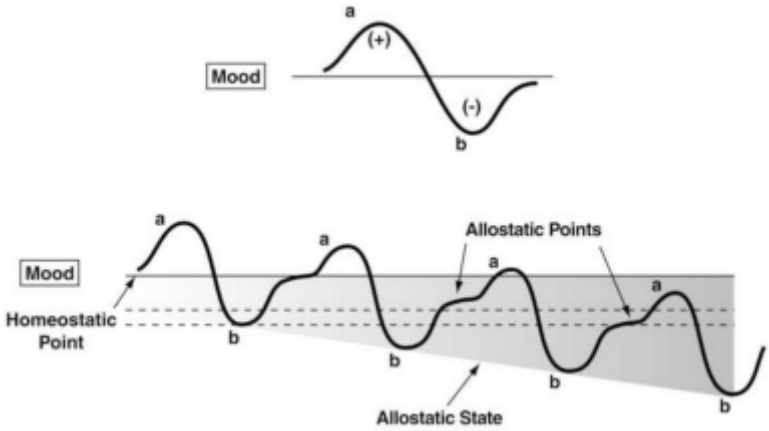


Figure 2: Progressive development of the anti-reward system from initial substance experience (top) to increasing dysphoria and allostatic load (internal physiologic stress) over time with repeated substance use. (Koob, G., 2015)

Just as progressive neuroadaptations develop over time, return to neurotypical functioning has been shown to fail to return to normal until months of abstinence have passed (Koob, G. and Mason, M., 2016). Time to return to normal function is multifactorial and includes the extent of anti-reward development and environmental stresses in recovery (Wemm, S. and Sinha, R., 2019). Portending precarious underlying neurobiology predisposing persons to relapse in the first months of abstinence, our framework expanded this through careful and often lengthy interviews with clients seeking greater insight surrounding prior relapse events.

Exploring the thought process prior to the decision over which people become 'powerless' in severe substance use disorder, that is taking the first drink or using a substance, revealed one commonality: while people could recall the circumstances surrounding the substance use, they most often had no recollection

of their thoughts immediately preceding consumption. It became quite apparent that there was a momentary conscious lapse, that the decision was made automatically. It consistently appeared as if some other part of the brain was making the decision and conscious thought was overridden. Returning to the iRISA model (Goldstein, R. and Volkow, N., 2001), neurobiological changes in the brain over the course of addiction had pushed inhibition beyond 'impaired' to 'complete,' meaning no conscious resistance whatsoever in many cases. This marked our first direct indication validating the veracity of AA's beliefs with neurobiology.

We then postulated that a discrete neural circuitto drive the fateful decision and actions, existed in the brain which had become empowered unto itself beyond conscious control. Furthermore, looking at the downward trajectory of people's lives in addiction, we portended this was associated with fundamental decision-making processes that became increasingly self-destructive. Decisions made over the course of addiction became geared solely to creating the conditions for the circuit to activate. Thus, there was a broader impairment in decision making which made life truly 'unmanageable.' Addicted persons had maladaptive brain executive function to the point of being unable to have enough clarity of mind to stop substance use without external help, barring an act of God. Exploring the thought processes of addiction thus gave a working hypothesis for the biology of Step One, powerlessness and unmanageability being the result of specific brain disorders.

Continuing to expand this hypothesis through deductive reasoning, we were aware of the crucial interaction among emotions and decisions (George, S. and Zane, B., 2016). If the purpose of emotions is not fully to motivate decisions (consistent with the meaning of its Latin root, emovere), at minimum, emotions strongly influence the nature of decisions people make. To explain the reason behind the breadth and compulsive tendency of addicted persons to make decisions which inevitably became destructive, we expanded on research on the limbic system (Goldstein, R. and Volkow, N., 2001; Koob, G. and Mason, M., 2016; Ceceli, A. et al, 2023; Feltenstein, M. et al, 2021) of the brain that had become severely maladapted.

In developing a model for the neural circuit that activated the irresistible compulsion to drink or use substances in severe addiction (DSM V), we believed that decisions corresponded with electrical activity within the brain. As such, a neural circuit could be represented initially as an electrical circuit and explored through this perspective (Iles, J., 2005; MacGregor, R., 1987; Singh, J. and Kapur, G., 2019; Cho, S. et al, 2021; Harrison, R. 2008). An NMOS transistor (Chin, A. et al, 2019) amplifier provided a working model:

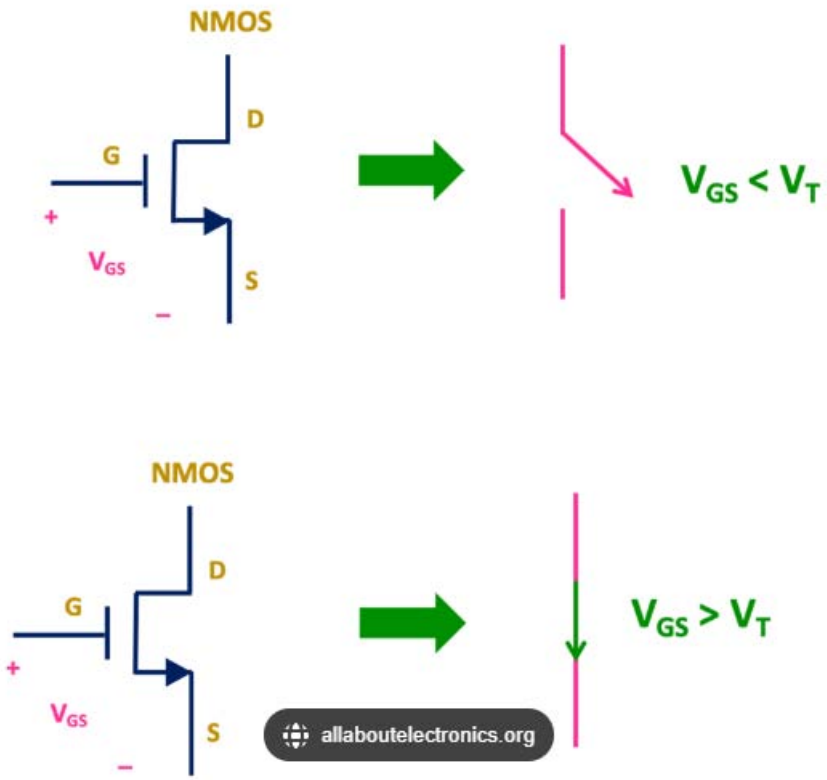


Figure 3: An NMOS transistor acting as a binary circuit: when the voltage at G, V_{GS} exceeds the threshold voltage for the transistor semiconductor, V_T, electricalcurrent travels through D to S

Depending on the material nature of the semiconductor (Chin, A. et al, 2019) and the polarity and strengths of the input, a small current at the emitter (D) can be amplified significantly at the output collector (S). In similar fashion we theorized that a small impulse to use substances could pass through a neural network analogue and become amplified to overpower all circuitry in the executive part of the brain. This would model the impulse to use substances at D, overpowering the inhibitory circuitry of the prefrontal cortex at G and producing an amplified output (to consume substances) at S. In neurobiological terms, the result would be powerlessness over the decision to use substances.

Given that this transistor-like amplifier circuit seemed so far beyond reach in the brain (most persons with addictions have tried many times to abstain and sought professional help often to no avail), our therapeutic target became the inputs (the prefrontal cortex, modelled by V_{GS} above). Should neurotypical function of the inputs be established, the internal circuit could potentially be brought under control. We also hoped that the actual physical composition of the semiconductor-like circuit at G would resultantly return to healthy.

From such reasoning did the union of neuroscience, 12 Step programs and counselling emerge. A concrete understanding of the neurobiological truth of Alcoholics Anonymous' Step One with counselling addressed at the inputs (thoughts, emotions and behaviors) offered a novel, potentially dramatically effective method of helping people afflicted by addiction.

Additional logical assumptions underscored what became the Step One approach: since we were dealing with the brain, the principle of neuroplasticity applied. Neuroplasticity has only become well accepted this century and refers to the modifiability of the brain (Innocenti, G., 2022). Changes in both structure and, consequently, function of the brain are inherent properties that occur throughout life with greater propensity for this in the young developing brain. Nonetheless, neuroplasticity occurs throughout the entire life span. It is not necessarily exclusively adaptive to external stimuli but can also be the cause of neurological and psychiatric pathologies (Innocenti, 2022).

Further logical hypothesis expansions were made prior to the rigorous research to explore our notions:given that addiction seemed to develop over time to eventually dominate behavior, neuroadaptations were most likely to be created within previously healthy circuitry. Addiction was not a separate neural circuit from the rest of the brain, rather it was fully integrated with maleficent neuroadaptationsin previous healthy networks. Without definitive healthy neuroplastic changes, the overall state of addiction would continue to exist. Of course, changes in structures and networks would be iterative and at times synergistic, leading to a non-linear progression. This fully matched our observations of persons over the course of recovery. The principles of neuroplasticity also offered the prospect of full recovery, as Alcoholics Anonymous had proclaimed in 1939 after only two years of its formation. A disorder could be reordered.

b) Basic Science Framework

With experience, observation and access to rigorous scientific articles available for our methodology, we explored models from several disciplines to form a framework for research. The American Psychiatric Association defines addiction as a complex condition – a brain disorder that is manifested by compulsive substance use despite harmful consequences. The limbic system itself is markedly complex both in structures and interconnectedness (Catani, M. et al., 2013; Volkow, N., Michaelides, M. and Baler, M., 2019), not to mention introducing neuroplastic changes (see Figure 4).

We chose to frame our exploration of the behavioural neuroscience of addiction through the lens of a complex dynamic system (Close, C., Frederick, D., Newell, J., 2002). A system is any collection of interacting elements for which there are cause-and-effect relationships among the variables. While a reductionist approach (Mazzocchi, F., 2012)is often used in complex systems and was an initial phase of our exploration, the systemic approach insists on an understanding of the interaction among variables in modelling. The specific system model under investigation was the transistor amplifier circuit, seen as having multiple, likely interconnected inputs and a semiconductor element with variable material composition. The term complexity refers to both the number of variables (inputs) and the interactions among all.

The descriptor, dynamic, in complex systems acknowledges that the variables and relationships among them change over time (neuroplasticity). In our case, changes may or may not be entirely adaptive to external environmental stimuli but are dependent on all other system elements. Fortunately, overall, there is relative stability of the system over days to months to years despite individual elements functioning in millisecond timeframes. With most neural network functioning at generally low frequencies (<100 Hz), current diagnostic methods in micro and macrobiology reveal considerable not only about structure but most importantly, function.

To date, we have identified numerous areas and major nuclei in the limbic system involved in addiction. Each of these have distinct subregions and multiple functions. Additionally, there are a number ofpotential physiological neuroadaptations at the neuronal level for

each neuron in the system. All areas and nuclei communicate with each other and information transmission integrity is subject to change although there is consistency in this aspect of neuroplasticity among all connections. Fortunately, the inter-element communication is dominated by a number of discrete pathways simplifying understanding in this regard. This array of intercommunicating elements with a brief description of each is found in Tables 1., 2., and 3. and illustrated in Figures 4., 6., 7. and 9.

Table 1: Structures and Areas of the Limbic System Implicated in Addiction

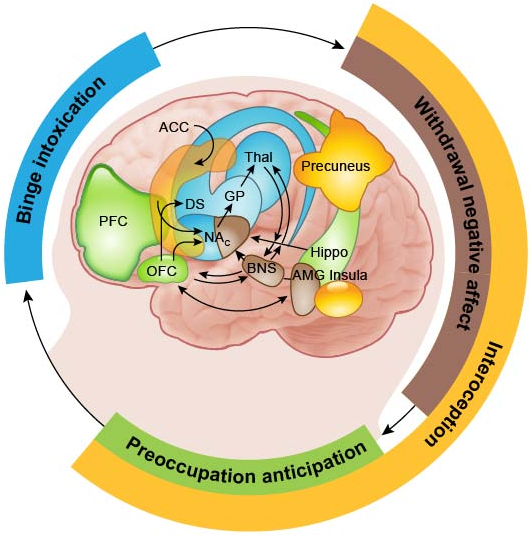
Limbic Element	Brief Function(s) relevant to Addiction	Neuroadaptations in Addiction
Amygdala	Signals fear, anxiety, aggression, anger, male sexual impulse	Grows in size, hyperexcitable and hyperreactive
Hippocampus	Memory associated with emotion, also regulates cortisol in stress response	In active addiction, new information storage declines except regarding substances
Hypothalamus	Signals stress response from limbic system to the body	Maintains an elevated, less responsive baseline function
Lateral Habenula (LHb)	Important in aversion behavior, amplifies negative input and signals back to rest of system	Becomes increasingly sensitized to substance cessation
Mammilary Bodies	Involved in transmission of memory information, reward prediction	Function declines, especially with alcohol
Nucleus Accumbens (NAc)	Motivation for reward, reward prediction error, limbic-motor interface	Increasingly blunted DA response, greater influence over motor as PFC declines
Prefrontal Cortex (PFC)	Executive control over decision making, emotional regulation, working memory and calculation/planning, risk/benefit	Decline in all functions, appears (by deduction) to focus more on substances
Rostromedial Tegmentum (RMTg)	Reacts to negative DA in VTA, signals LHb, aversion	Responsive to substance cessation, temporarily relief if substances planned
Thalamus and Insula	Distributes external and interoceptive (Insula) stimuli to rest of system	Some literature points to preferential bias to transmit substance related information
Ventral Tegmental Area (VTA)	Signals want or need to NAc through DA efferents	Increasing response to substance related cues

Table 2: Communication Pathways Involved in Addiction

Communication Pathway	Major Elements Connected (note pathways are bidirectional)	Function
Mesolimbic pathway	VTA to NAc	Physiological DA response
Amygdalofugal Pathway	Amygdala to Hippocampus	Automatic fear response
Hypothalamic-Pituitary-Adrenal Axis	Rest of limbic system signals Hypothalamus	Stress response
Medial Forebrain Bundle	PFC to all elements of limbic system	Emotional regulation, executive decision making
Mesocortical Pathway	PFC to NAc	Reward prediction & analysis, executive decision input

Table 3: Mechanisms of neuroplasticity

Neuroadaptations at cellular level (neuroplasticity mechanisms)	
1.	Mitosis (cell duplication in younger people)
2.	Myelination or demyelination (affects transmission among neurons)
3.	Synaptic growth or recession
4.	Dendritic branching (recession or growth)
5.	DA receptor up or down-regulation
6.	DA transporter up or down regulation
7.	DA reuptake up or down regulation



Where: PFC represents Prefrontal Cortex, OFC is orbitofrontal cortex (within the PFC in our model), ACC is anterior cingulate gyrus, Thal is thalamus, Hippo is hippocampus, DS is dorsal striatum

Figure 4: From Volkow, N., Michaelides, M. and Baler, M. (2019). The Neuroscience of Drug Reward and Addiction

What seems a near impossible task to consolidate and understand is made manageable through, first, a reductionist approach identifying anatomy and function of the specific elements. Fortunately, there is general uniformity of basic neuronal structures and networks, as well as commonalities of thinking, emotional and behavioural patterns of addicted people. Most of our clients, virtual or residential, are able to grasp an adequate understanding of this material and self-insight within 45 days to establish sustainable recovery.

c) *Specific Findings*

We explored our model of an NMOS amplifier transistor as the decision circuit at the centre of addiction, in the context of consensus surrounding the neurobiology of addiction being dominated by 'the dopamine hypothesis.' This was put forward convincingly by a pioneer of addiction neuroscience, George Koob of The Scripps Research Institute (Koob, G., 1992). This hypothesis has been the focus of significant research to present day and remains the most popular theory underlying the neuroscience of addiction. Addictive substances are classified as such because they all create a dopamine rise in a part of the midbrain (assuming the triune brain anatomically) termed the nucleus accumbens (NAc).

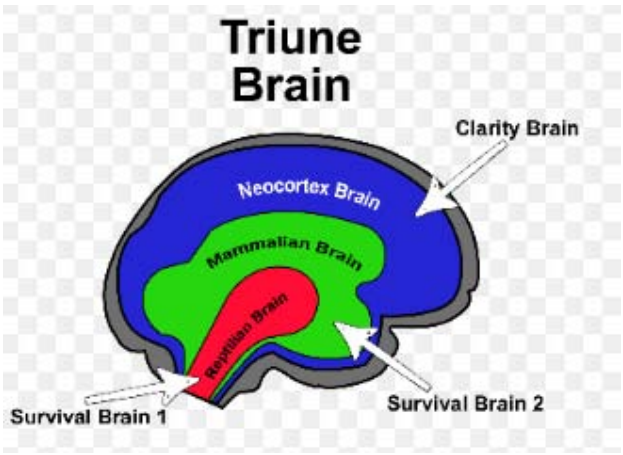


Figure 5: The triune brain schematic

A rise in dopamine is temporally associated with the high of addictive substances. The dopamine system projecting to synapses in the NAc is still considered by most to be the center of reward, the reward system. This view is unfortunately incomplete when one explores further the complexity of addiction. We also believe that the prevalence of theories which emphasize an uncontrolled reward system as a fundamental issue

thatcontinues to maintain societal stigma of addiction.Through considering persons become so addicted to the reward of substances that they don't want to stop, implies continued choice on the part of addicted persons.

Through a reductionist framework, we deducted that it was an excess of dopaminergic neuron excitation, V_{GS}, (compared to inhibitory neurons, V_t) that ultimately activated the circuit to use substances as modelled by the NMOS transistor (Figure 3.).

An exploration of the dopamine (DA) neuron reveals much when considered in the experiential context of addiction. In brief, chemicals including addictive substances bind to receptors on dendrites (they look like Christmas trees) on the cell body and create electrical charge which then creates an electrical current which travels down the axon. Axons are insulated with myelin and the electrical charge, on reaching the pre-synaptic terminal, activates dopamine transporters (DATs) (see Figure 7.). DATs then bring vesicles of dopamine (like bubbles containing DA) to the membrane and release DA into the synaptic cleft. In this space, DA then binds to dopamine receptors (DARs) of the next neuron. In the binding process, Ca+ molecules are released. This leads to accumulation of positive charge in the post synaptic terminal and an electrical current which then travels down the axon of the ensuing neuron. This simple model explains how substances which activate one neuron then turn on the next neuron in the neural network, which could be, say, the experience of reward.

Recall that we are considering the midbrain which is accepted to be essential for survival through maintaining physiological stability referred to as salience. Clearly, addictive substances, which dramatically elevate DA levels and transmission, threaten salience. In a response to 'control' the dopamine response and maintain salience, through mRNA transcribed through genes in the nucleus, the neuron creates proteins which, at the synapse (Sulzer, D., 2011):

- Down-regulate DATs
- Down-regulate DARs; and,
- Up-regulate DA reuptake transporters

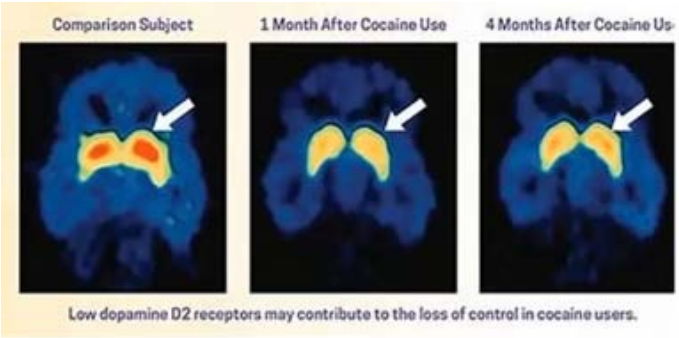


Figure 6: D2Rs (DA2 Receptors) in cocaine users. Harvard Medical School (2021). Understanding Addiction

As a result, over time, more of the substance is required to achieve the same electrical energy as occurred with the first experience. Additional adaptations which the neuron can perform are duplicating itself (in developing brains, mitosis) and change dendritic configuration. Advanced substance use can also affect the integrity of the myelin sheath, giving rise to conductive loss and crosstalk (Ashton, C. & Duffie, D., 2022). Finally, the neuron can create new synaptic connections when so stimulated, a process referred to as Hebbian plasticity (Turrigiano, G. and Nelson, S., 2000).

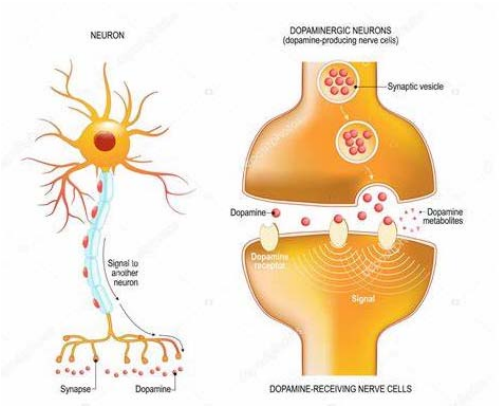


Figure 7: Schematic of the dopamine neuron and synapse

A few fundamental associations can be made through an understanding of neuroadaptations at the cellular level. Clearly, neurons can and do change through distinct mechanisms. Summarily, these help to demystify neuroplasticity in very simple terms. Second, a quick study of the neuron informs us about the science behind tolerance to substances which all addicted persons develop over time. Finally, this contributes to an understanding regarding the 'powerless' aspect of Step One and the inability to stop at one drink when driven to reach previous euphoria (trying to achieve the previous dopamine high in the face of resistant circuitry).

d) The Drive Towards Substances: The Nucleus Accumbens And Ventral Tegmental Area

Assuming the neural circuit to consume substances exists in the dopaminergic system within the nucleus accumbens, further proof of this mechanism as well as identification of inputs forms the next logical exploration. We were guided by much superb literature on the reward side of addiction (Volkow, N., Michaelides, M. andBaler, R., 2019)., as well as partially conflicting literature surrounding the NAc in isolation (Floresco, S., 2015). There is good research confirming that the NAc is not simply a 'reward centre' responding proportionately to dopamine afferents. Rather, it is far more sophisticated and functionally aligned with the powerlessness aspect and narratives given and described as: 'there was always the curious mental phenomenon that parallel with our sound reasoning, there inevitably ran some insanely trivial excuse for taking the first drink (AA Basic Text, 1939).'

Returning to the triune brain model, the NAc is a deep structure within the survival-geared midbrain. Executive thought and consciousness are generally accepted to exist in the frontal cortex. Floresco (2015) in his broad review states that the current emphasis on the NAc being the reward center has veered from the more generalidea initially proposed by Mogenson (Mogenson et al., 1980) that this region serves as alimbic-motor interface. Emerging evidence further supports the NAc as having diffuse projections of axons to cortical motor areas (Salgado, S. andKaplitt, M., 2015; Sawada, M. et al, 2015; Miyachi, S. et al, 2006). Additionally, while the focus is generally on the projections from the Ventral Tegmental Area (VTA), where the dopamine cell bodies reside, to the NAc, little is made of the bidirectionality of circuitry between the VTA and NAc.

Corkrum et al (2020) speak strongly to this as well as Floresco (2015) and Yang et al (2017). Logically, bidirectional communication better explains the actual functionality of reward driven behaviour as well as aversion (which will be explained later). While NAc dopamine synapse activation is seen in anticipation and reward experience, we suggest that the hedonic experience takes place through further projections to the basal ganglia and ventral pallidum (there are few known neurotransmitter sites typically associated with the pleasant feeling of reward within the NAcitself) (Root, D. et al, 2015; Castro, D. et al (2015). With the VTA accepted as signalling 'want or need,' it makes most sense that major inputs to create this emanate from the NAc as Corkrum et al (2020) suggest.

We suggest a primary role for the NAc as a dopamine regulator to maintain salience, and a motor interface (mediated of course by the PFC). Dopamine itself in the mesolimbic system (VTA and NAc) then also acts as a motivator of action for which there is much good evidence (Wise, R., 2004). Significant for our understanding of addiction is the NAc function of measuring reward prediction error (RPE), essential to learning and memory (Yang et al, 2017). This argument for the multiple functions for the NAc and VTA will make further sense as we consider the role of avoidance (we term 'the anti-reward system') as equally significant as the positive reward system in addiction.

We know that as addiction develops, there is progressive decrease in reactivity of DA synapses in the NAc. Termed tolerance, there is increasingly less response in the NAc for the same dopamine signal from the VTA as the mesolimbic system strives to maintain salience. Additionally, in advanced addiction, numerous authors (Corkrum et al, 2020; Febo, M. et al, 2018; Koob, G. and Mason, M., 2016) suggest a deficit in extracellular dopamine creating what is functionally a hypodopaminergic state in advanced addiction. Returning to Step 1, this is a major contributor to craving as experienced as part of the powerless over addiction phenomenon.

People with severe addictions will admit being unable to perform even the most minor activities of daily living, let alone function at all in a work environment without substances. This is unfortunately true physiologically: in severe addiction, the hypodopaminergic state resulting from resistance which has developed in the neural circuitry along with potentially low basal extracellular dopamine levels has a devastating effect on motivation.The simplest things such as showering and getting dressed seem like a monumental task without topping up on substances.

While this may appear as a willful lack of care of self or a manifestation of self-loathing on the part of severely addicted persons, they simply do not have the motivational energy through the NAc. This terrible phenomenon is in addition to the relentless emotional and thought dysphoria persons experience. In a complete hijack of healthy functioning, the limbic system hasnow equated substances with survival, as only substances will provide the necessary dopamine response to feel functional.

e) *Failure to Inhibit the Drive to Substances: The Prefrontal Cortex*

The limbic system, and those elements specifically involved in addiction, is a complex dynamic system unto itself whose purpose is the maintenance of homeostasis. Homeostasis can be considered persistence of a living system and society in a state of specified and dynamic disequilibrium (Pross A., 2012). System wise, the interconnected limbic elements can be thought of as alternatively competing and cooperating with each other in active striving towards a persistent and specified orderliness (Turner, J., 2019). Viewed as an internal environment, the limbic system maintains homeostasis through adaptive interfaces (the various elements), which monitor external environments.

As a living, closed thermodynamic system unto itself, geared to maintaining the greater intracorporeal entity, energy is continuously required to survive in a dynamic environment. Knowledge and cognition are equally needed within the limbic system to construct cognitive representations of the environment in which it is embedded, with knowledge of what the contained environment should be, and continuously seek reward to maintainhomeostasis in the face of ongoing perturbations to it (Feldman Barrett, L., 2006).

Implicit in this reward seeking function and processing external cues is the Nucleus Accumbens. As one of its critical functions, the NAc calculates reward prediction error (RPE) (Floresco, S., 2015) whereby positive RPE drives anticipation, motivation towards and memory of reward events. The primary neurotransmitter involved in RPE is, of course, dopamine. Resultant neurocircuitry of the midbrain in reward seeking and survival are motivation to activities, behaviours and external substances that result in dopamine increases in the mesolimbic system. Emotions are created through this process.

In simple terms, the elements of the limbic system react to internal and external stimuli, process it through intercommunication including the PFC to drive the mesolimbic system to drive decisions to maintain overall dopamine homeostasis, in an energy efficient manner as possible. Equally, the system creates negative RPE to direct diversion and avoidance.Proof of concept is highly supported by reviews of Deep Brain Stimulation (DBS) for addictions which is aimed at the Nucleus Accumbens (Chang et al, 2022). Electrical stimulation of the NAc through DBS acts as a system override of the rest of the contributions to the NAc of the limbic system.

Addictive substances and behaviours in vulnerable people all produce a positive rise in dopamine levels in the synapses of the NAc. This rise can be multiples of baseline levels and result in significantly elevated RPE initially on consumption. Regardless of input from the PFC, the midbrain interprets substances as contributing to positive valence (Feldman Barrett, L., 2006). Despite societal beliefs influencing the PFC to inhibit substance use, the midbrain is susceptible to dominate the decision-making process and repeat the experience. In such a manner, addiction progresses to reach the widely accepted three-stage cycle of addiction as described by Koob (2001), Volkow (2018) and their associate researchers.

While acknowledging that participation and influence from other limbic structures is continuously present, focusing on the basics of the neuroscience involved in Step 1 does not detract from the veracity of this hypothesis. During the last decades, many studies have shown that addiction results in heterogeneous cognitive deficits (Pitel et al., 2023), including impairments of executive functions, memory, visuospatial abilities, difficulties in emotionalprocessing, and theory of mind (ToM) abilities (Le Berre et al., 2019). ToM is defined as the capacity to infer mental states from others' social signals to predict their behaviors, desires, intentions, and beliefs.It is now well-known that attention, working memory, and executive functions rely notably on the prefrontal cortex (Maillard, A. et al, 2020).

Executive functions are cognitive abilities that control and regulate the emotional (survival) system to coordinate thoughts and actions toward a goal. Executive functions include mental flexibility, abstraction, planning, problem-solving, shifting of mental states, monitoring and updating of working memory representations, organization, rules deduction, reward delay discounting, and categorization (Maillard, A. et al, 2020).

There is a considerable and emerging literature concerning the role of the prefrontal cortex in emotional regulation, much of it focussing on the PFC and amygdala communication (Suzuki, Y. and Tanaka, S.,2021;Dixon, M. et al, 2017). Unfortunately, less research has been performed regarding the relationship between the PFC and the nucleus accumbens. The connection between the two is referred to as the mesocortical pathway. Within the mesocortical pathway, the anterior cingulate, prelimbic cortex, and orbital prefrontal cortex (OFC) have been accepted as being involved in the regulation of emotional responses, cognitive control, and executive function (Volkow et al. 2019).

Much of the literature points to neuroadaptations in the various aspects of the PFC as leading to persistent addictive behaviors, including the devaluation of natural rewards, diminished cognitive control, and hyper responsiveness to drug-associated stimuli (Koob, G.andLe Moal, M., 2001; Kalivas and Volkow, 2005; Carelli and West, 2014). Generally, the view continues that changes in the PFC contribute to escalation of substance use through mediating conditioned responses, drug craving, and loss of behavioral control (Feltenstein, M. et al,2021)

In light of our observations of clients with severe substance use disorder over the first 30 to 45 days of recovery (abstinence), neuroimaging studies(Goldstein, R. and Volkow, N., 2011) and additional studies focusing on the effects of chronic stress and substances on the PFC (Koob, G. and Schulkin, J., 2019), we offer an alternative view which is best observed in recovery.

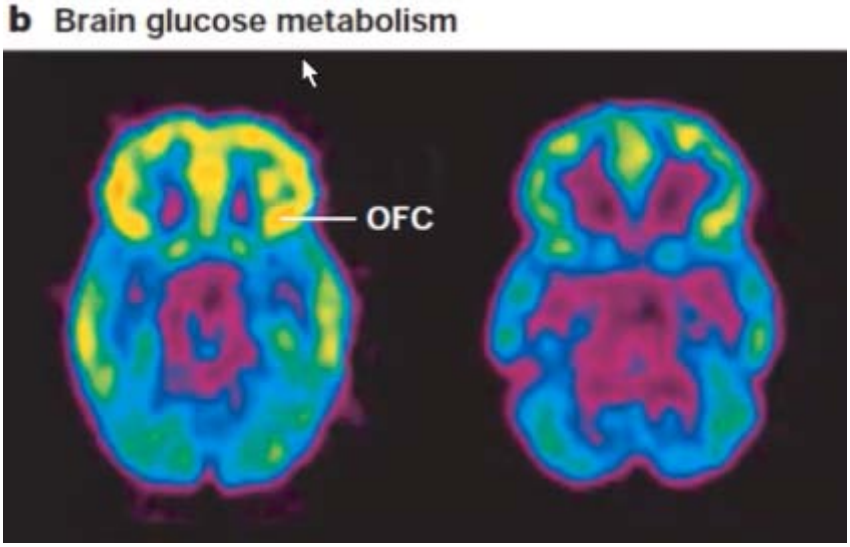


Figure 8: Harvard Medical School (2021). Understanding Addiction. OFC refers to orbitofrontal cortex

As shown in the scan above, neuroimaging studies reveal an emerging pattern of generalized prefrontal cortex (PFC) dysfunction in drug-addicted individuals. This worsening PFC hypofunction is coincident with more drug use, worse PFC-related task performance and greater likelihood of relapse. Widespread PFC activation is seen in drug-addicted individuals upon taking cocaine or other drugs and upon presentation of drug-related cues. We believe that this is compatible with dopamine surges from the NAc and VTA to the PFC, which then creates a transient focus on obtaining the drug of choice or otherwise. We additionally purport that a degree of PFC dysfunction precedes drug use, creating vulnerability for susceptible persons in developing substance use disorders.

Secondly, studies in neuropsychopharmacology demonstrate the molecular effect of stress hormones (Corticotropin Releasing Factor or CRF and cortisol) and substances together and alone in SUD (Wemm, S. and Sinha, R., 2019).

Accordingly, we assert that rather than PFC adaptations as exclusively pursuing substances (which is true to a small extent), the major issue is with the loss of PFC ability to regulate, and specifically inhibit, emotional andmotivational drive from the midbrain. This is well observed as well as is partial recovery of the PFC in our clinical experience. Much of the behavioural impulsivity and extremes in emotions and compulsions seen in early recovery (ask anyone at AA about this phenomenon) is in large part due to loss of PFC inhibitory function.

In cognitive testing using the Creyos platform™, a robust assessment tool developed through combining neuroimaging with neuropsychological studies, clients uniformly scored well below average in virtually all domains regardless of their backgrounds. Fortunately, at the 30 day mark, cognitive scores improved to normal in general. Additionally, scores using Muse 2 ™neurofeedback meditation for 15 minutes daily improved substantially over the time in residence with us. This also supports PFC reactivation, a key goal of our program.

Interestingly and of tremendous clinical significance, Muse 2 scores declined greatly for all clients consistently over atwo-day period at our centerbetween 8 to 14 days from admission. Prior to Muse 2, the period from 8 to 14 days had been a time where clients would regularly insist on self-discharging, suffer severe anxiety at times and exhibit fully irrational thinking. We believe that this period refers to the time whereby the hypothalamus begins to resume normal activity (Ashton, C., 2014) and the resulting stress response is excessiveuntil the hypothalamus achieves a new baseline activity over 2 days.

Emotional management including impulsivity is a challenge for both staff and clients, particularly in the first two weeks in residence. Also frustrating to clients is loss of working memory and inability to remember educational material, as well as orientation to place from one day to the next. Again uniformly,working memory returns dramatically for clients (much to their relief) around 18 to 20 days in the program.

To a large extent, this severehypo functioning of the PFC explains powerlessness due to lack of inhibition over the NAc. Further research adds to understanding the magnitude of the drive to obtain substances and associated high risk behaviours. It is much more than a lack of inhibition and a notion which is slowly becoming more recognized in the scientific community (Ashton, GAB 2024). Recall the NMOS transistor amplifier model: in addition to acting as a binary circuit, the semiconductor is fully capable of amplifying the strength of the input signal. Strength of amplification depends on collateral inputs and the physical properties of the semiconductor.

Similarly, the decision toobtain and consume substances in persons with severe addiction often overwhelms any thought of consequences. This is the point where otherwise unconscionable acts are undertaken in substance use disorder, often resulting in severe, traumatic consequences as well as imbedding a seemingly hopeless level of shame.

In pursuit of understanding this third element creating powerless in severe addiction, we undertook to find the neurobiology which amplifies motivation to consume substances. Simple Pavlovian learned behavior is considered a fundamental process in the development of substance use disorder of which there is much literature (Day, J. and Carelli, R.,2007; Heinz, A. et al, 2019). On this basis, we explored the dopamine profile in the mesolimbic from steady state to being cued (small release of DA) to the full DA spike experience corresponding to reward.

It is well known in Pavlovian learning, this process becomes embedded such that reward is experienced in the mesolimbic system prior to the actual consumption and physiologic DA spike. This corresponds to narratives given by many clients that the anticipation of reward is often higher than the consumption experience itself. Additionally, if they do not experience the rewarding feeling anticipated, they become agitated and dysphoric. Complete omission of the reward following experiencing the high of anticipation results in further, often deep dysphoria. This phenomenon is articulated beautifully and termed reward prediction error (RPE) by Keiflin, R. and Janak, P. (2015).

RPE remains fundamental to the development of addiction. Assessment of a potential reward is predicted within the NAc through receiving information from other limbic areas and the cerebellum. This forms a prediction of the reward. What is physiologically the actual result of the behaviour or substance (i.e. the DA response) is measured as well by the NAc calculating reward prediction error. The magnitude of RPE (positive or negative) results in proportional glutamate projected to the hippocampus, as well as the VTA, facilitating encoding of memory. Simply put, the brain remembers things that are unexpectedly better than anticipated (+RPE) to be able to repeat again. Equally, the brain remembers things which resulted in an experience worse than predicted (- RPE) to avoid repeating (avoidance learning).

Often termed the anti-reward system (Koob, G., 2015; Borsook, B. et al, 2016), this third element in powerlessness is as, if not more, influential as the reward seeking aspect in severe addiction. Negative DA states (Wise, R. and Robbie, M.; Keiflin, R. and Janak, P., 2015) are highly unpleasant and feel excessively fatiguing. There seems no healthy, fast way out of this state, barring external substances.

Reward omissions, as well as aversive outcomes, activate neurons in the lateral habenula (LHb) (Matsumoto, M. and Hikosaka, O., 2007), which indirectly inhibits DA neurons via activation of GABAergic neurons in the rostromedial tegmentum (RMTg). A role for involvement of the LHb in negative prediction errors has been established in animal studies (Keiflin, R. and Janak, P., 2015).

It is acknowledged that reduced activity in a large subset of dopaminergic projections to the nucleus accumbens is associated with aversion. Optogenetic inhibition of ventral tegmental area dopamine neurons produce avoidance of associated places and cues, an effect that depends on DA receptor signaling (Danjo et al., 2014). Inhibition of these neurons via DA receptor activation causes a conditioned place aversion and gives rise to negative affect (Liu et al. 2008). Aversive stimuli of various sensory modalities broadly inhibit dopamine release in the VTA and NAc (de Jong et al., 2018; Menegas et al., 2018).

This is considered a fundamental mechanism for aversion, a function necessary for survival. To put the neurobiology of addiction in perspective,recall our discussion on the mesolimbic pathway. This becomes so severely maladapted that substances are interpreted as necessary for survival. Following that logic, the severely addicted brain now sees absence of substances as a threat to survival and accordingly imposes its avoidance system to deter the person from stopping substance use.

At the prospect of abstinence, it is typical for addicted persons to respond with panic and often anger automatically as the avoidance defence manifests. Unexpected inability to obtain and consume substances is met with an often-prolonged state of severe dysphoria in severely addicted people. Superimposed on a hypodopaminergic state is sudden absence of substances followingan anticipatory state, resulting in a negative dopamine spike (Keiflin, R. and Janak, P., 2015). This appears most relevant to the rostromedial tegmental nucleus (RMTg) aspect of the VTA, an area highly associated with registering and encoding aversion (Jhou, T. et al., 2009) which signals inhibitory control over DA neurons in the VTA.

The RMTg is located adjacent to the lateral habenula (LHb). There is a recently emerging literature surrounding both the RMTg and LHb which explains neurobiologically the terrible drive behind addiction (Suzuki, Y. and Tanaka, S., 2021). Simply put, in healthy persons, aversive stimuli activate lateral habenula neurons which, in turn, inhibit dopamine releasein the VTA and mesolimbic pathway, thereby inhibiting positive action and creating aversion. As previously identified in this paper, two elements bear heavily on the science of powerless: reduced dopamine response (a chronic hypo dopaminergic state) and a faulty prefrontal cortex, unable to control impulses to consume substances.

The amplification of drive emanates from the LHband a 180^0 hijack of the avoidance system. As addiction progresses, the dopaminergic mesolimbic system has been so fundamentally maladapted that it associates substances (natural rewards no longer are able to produce needed dopamine response) with survival; conversely cessation of substances is equated as a crisis to be avoided at all costs. This is particularly evidenced clinically in acute withdrawal, most noticeably in alcohol, opiate and benzodiazepine withdrawal. The pain, dysphoria and physical symptoms from activation of the anti-reward system become progressively severe to the point of becoming unbearable for persons with severe addiction.

With multiple episodes of full or partial acute withdrawal occurring over development of addiction, the anti-reward system becomes increasingly 'kindled' (Breese, G. et al., 2005), meaning increasingly sensitive and hyperreactive to negative stimuli. This is due in large part to the LHb becoming increasingly fierce in its response through progressive neuroadaptations due to stress and substances. While not completely understood (it is hypothesized that cell membrane changes are responsible (Authement, M. et al., 2018), progressive adaptations in the LHb create amplification of negative stimuli (Graziene, N. et al., 2018). This produces increasing distress with each attempt at stopping substances, an experience virtually all addicted people will attest to if they've had multiple attempts at quitting.

With responses to negative stimuli already magnified in other areas of the limbic system (the amygdala and hypothalamus particularly), this is then amplified by the LHb creating unbearable dysphoria. As well, with the kindling effect and dysphoria experienced with withdrawal episodes, this creates learned behavior to avoid abstinence in severely addicted people. Clinically, for persons in the contemplative stages for recovery, it is not uncommon for them to say they feel like they will die if they have to quit substances. For the caring professional, it is most helpful that this seeming complete irrationality is not driven by a compulsion to get high. Rather the anti-reward has created this level of thorough distortion neurobiologically: what appears as ambivalence regarding quitting, is truly an excruciatingly frightening prospect for the addicted person.

While not necessarily described by the DSM 5, it our firm belief that, over the course of development of substance use, the anti-reward system becomes dominant over reward and presents a daunting challenge for caregivers to support the client in overcoming this challenge. Typical for addiction, the level of discomfort anticipatedby addicted people in quitting substances is of tenhigher than the experience of withdrawal it self. Given this shift to the major obstacle now being anti-reward and with concurrent diminishing of the reward system, clients will now generally admit to using substances to function, to try to feel and act normal, and to not get physically and mentally sick.

II. Discussion

Understanding severe addiction through a neurobiological lens is most helpful in informing caregivers of what is actually happening in the addicted persons world at that time. Given the advancement and failure of healthy decision-making processes, it is easy to become enrolled in trying to understand the chaotic situation addicted persons' lives have become, to make sense of this complexity. Understanding this neurobiology then gives evidence and a lens for the counselor to focus their best modalities to support the person out of ambivalence and make the decision to cease substances.

The first part of Step One of Alcoholics Anonymous, we admitted we were powerless over alcohol, now has a concrete neurobiological explanation and proof of veracity. Three separate main processes converge to not only making cessation seem impossible and unwanted, but also an overwhelming neural energy to consume:

1. Severe hypo functioning of the prefrontal cortex;
2. Resistance developed in the mesolimbic circuit to experiencing positive reward; and,
3. Amplification of negative valence by the anti-reward system.

The poorly functioning prefrontal cortex simply does not have the electrical inhibitory power to stop the consumption drive created by the reward and, later, the anti-reward system.

As most alcoholic and addicts will verify in substance use disorder, the immediate thought process prior to acquiring and consuming substances cannot be recalled in any detail. The midbrain has completely taken over conscious thought; most people with addictions when questioned in detail will speak of some unknown sort of force carrying them through the acquisition and consumption phase. At best, they will report some internal chatter (PFC) suggesting that it was not a good idea but did not have the force to overcome the strange drive.

Given the extent of neuroadaptations which have occurred, it then becomes easier to understand and validate the often-unbelievable narratives we hear in addictions counselling. As an example, I received a distressed call from a young professional man who had finished our program and returned home 3 weeks prior to the call. He told me that he was sitting at his kitchen table with an unopened bottle of spirits in front of him. He had no recollection of driving to the liquor store and making the purchase, but acknowledged that somehow, he must have. Recall that the NAc has connections to the motor cortex.

The man had found himself on returning home suddenly under extreme family stress which included involvement of the justice system. Stress hormones, particularly CRF and cortisol, impair prefrontal cortex functioning in similar manner to substances in severe addiction (Sequeira, M. and Gourley, S., 2021).; Wojdala, A., Molins, F. and Serrano, M., 2020).In this man's case, stress had overwhelmed the PFC to such an extent that the NAc was able to completely hijack his actions: he had travelled and purchased the bottle without conscious awareness of what he was doing, let alone the potentially tragic consequences.

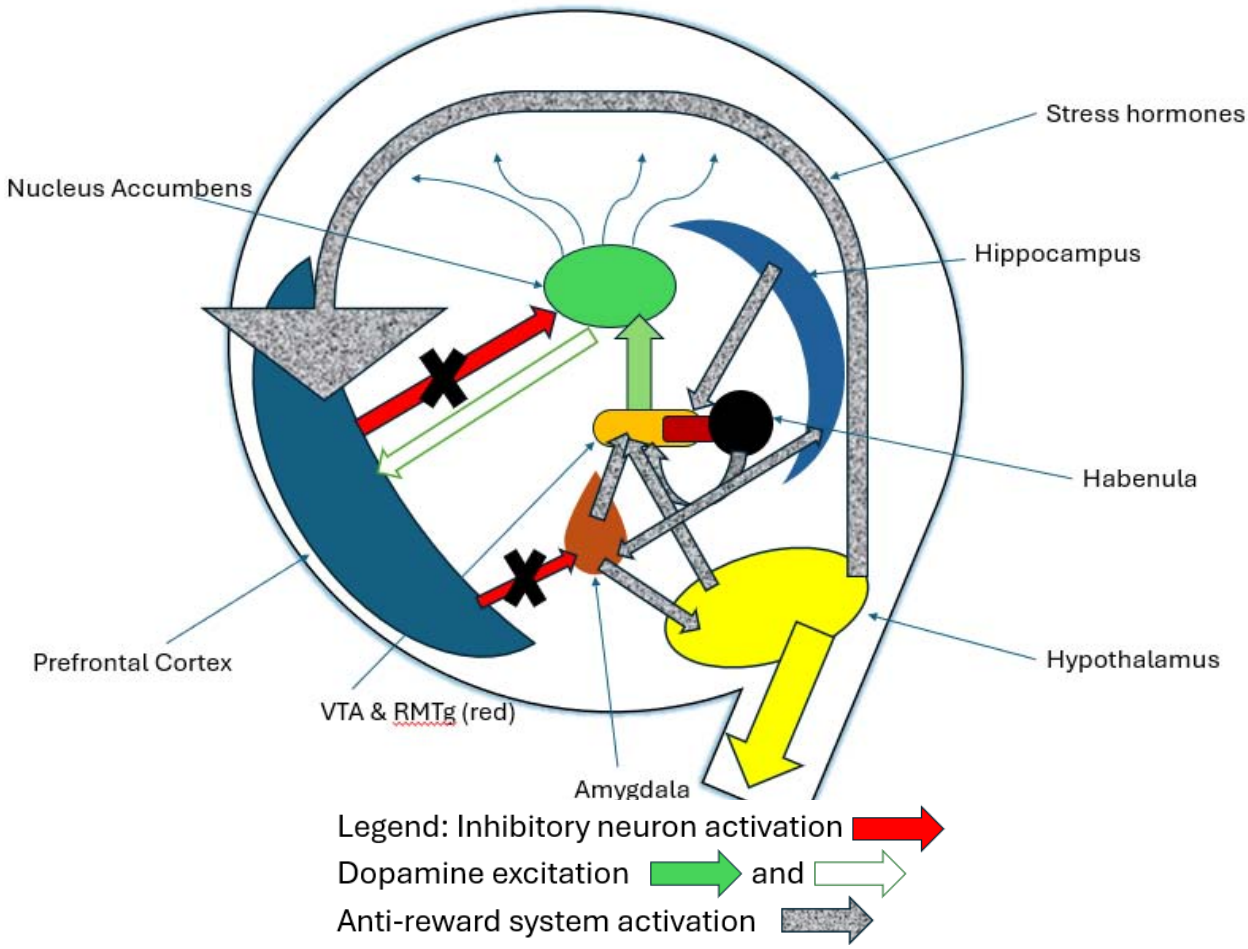


Figure 9: The Powerlessness Circuit. PFC: Prefrontal Cortex, showing disempowered inhibitory (X) influence over a. Mesolimbic (reward) pathway of VTA (ventral tegmental area), RMTg, (rostromedial tegmentum) projecting to Nucleus Accumbens,and b. Anti-reward system main parts being Amygdala, Hypothalamus, Hippocampus, and Lateral Habenula. Result is anti-reward and mesolimbic pathway in full control.

While a striking example of full hijack of the brain by the NAc, his experience is all too common in severe addiction and early recovery. Physiologic stress is always the cause underlying return to substances both in early and later recovery (Koob, G. and Schulkin, J., 2019) and a tremendousimpediment to recovery of neurotypical brain function. Counselling canbe exceptionally effective at reducing allostatic load through facilitating new perspectives and solutions.

Unless one is very experienced in the field or has had lived experience with addiction, the irrational self-destruction seen is very difficult to comprehend or validate. Moreover, as substance use disorder has also affectedmost of the rest of the limbic system structures, thoughts, perceptions, explanations and actions

become increasingly distorted. Emotions which are typically a challenge for everyone in life, now become neurobiologically distorted by the structures and system which creates them. For addicted persons, the false thought process becomes fully illogical in that what they firmly believe is keeping them alive is actually bringing on a premature and painful death.

Demystifying powerlessness in addiction is generally met with great relief by clients coming into recovery. It gives concrete answers to a seemingly incomprehensible constellation of symptoms, behaviors and actions that defy rational thought. Understanding the neurobiology of addiction can reduce the persistent self-shaming people in addiction and early recovery experience, as well as allowing clients to focus on the processes that definitively facilitate brain recovery.

Neurocounselling, Step One Therapy, is predominantly educational and focused on giving clients an understanding of what addiction truly is so that they can see its dominant influence on their life and reverse its course over time. Counselors trained in the behavioural neuroscience of addiction are able toeffectively facilitate client self-insight into their past and lingering inability to make healthy decisions, knowing that addiction remains a potentially dominant force in early recovery. The educational process to facilitate the client arriving at a level of insight to accept the neurobiology of Step One as tangible, requires proficiency in near all the current counseling modalities. Even though insight is being developed, return to neurotypical brain function does take time and patient understanding is vital to maintaining the therapeutic relationship. Self-disclosure or examples are used often and cautiously to illustrate how the disorder functions. Alcoholics Anonymous employs self-disclosure as large part of its program to effectively illustrate common purpose and belonging among its members.

III. Conclusions

The intent of this paper has been to unify two different schools of thought for treating addictions through the common denominator of behavioural neuroscience. This provides a common link between the counselling profession and self-help groups, demonstrating their compatibility and potential synergy. For the counselor, understanding the truth of the first part of AAs Step One, 'We admitted we were powerless over alcohol', gives further support to this community program and enriches the knowledge base for employing the various counseling modalities. Seen through the lens of behavioural neuroscience, counselors can interpret client issues in a precise fashion without being impeded by trying to interpret what is believable or not. What we term neurocounselling has definitive aims and processes:

1. Understand the robust neurobiology and associated behaviour patterns of Step One;
2. Through self-disclosure, examples or reflections of client experience, facilitate the client's understanding of this disorder and its outcomes within their own lives;
3. With addiction framed as a neurobiological disorder developed over a lifetime, facilitate client understanding of the actualeffect of circumstances and resultant behaviours over their lifetime to date (Dodge K. et al, 2009); and,
4. Support recovery of the prefrontal cortex and promote neuroadaptation of the reward system to healthy through positive life changes and experiences.

With the evidence presented herein, we are hopeful that this serves as evidence to unify approaches to care for persons with addiction through a new and more effective paradigm of neurocounselling. Our Step One Therapy approach encompasses a fundamental element of the Alcoholics Anonymous program, as well as its frequent use of self disclosure. Best practices in counseling modalities are fundamental to be able to maintain a positive therapeutic process and teach the underlying neuroscience.Understanding neuroplasticity gives tremendous hope to persons seeking recovery in that healthy functioning, unencumbered by addiction, can be the result over time. With reducing physiologic stress and allostatic load being a concurrent goal of therapy, counselors now have a far more focused approach than sifting through a constellation of issues.

Part 2 of this series will address the second part of AAs Step One: that our lives have become unmanageable. As written in 1939, this suggests that addiction is a progressive disorder to reach a point where life becomes unmanageable by the addicted person. Through combining neurobiology, genetics and environmental stresses we argue that addiction is a progressive disorder that occurs over a lifetime. Fundamentally, we see addiction as a progressive disorder of decision making. Seemingly rational choices made, often well before becoming addicted, set the life circumstances and internal conflictsnecessary to cause disorder progression. Decisions become increasingly unhealthy as do life circumstances to the point where addiction fully dominates brain function and affected persons are unable to see a path out of it.

While we admit that we have given a very brief summary of very robust neuroscience, exploration of the aggregate references herein supports proof of concept. Ultimately proof of concept exists for the vast majority of clients who have engaged in our program. Fortunately, in the five years of refining this method clinically, we are now able to fully expect that most people we see will experience sustained recovery and reclamation of lives that were once on the precipice of tragedy.

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Peptides and Lysine: New Therapeutic Frontiers in the Fight Against Alzheimer's Disease

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Abstract- Alzheimer's Disease (AD) is a prevalent neurodegenerative condition, affecting millions of people globally, particularly in an aging population. It is characterized by the aggregation of beta-amyloid and tau proteins, leading to the progressive loss of cognitive functions. This study investigates the therapeutic potential of peptides and the amino acid lysine in modulating the pathological processes of AD. The methodology included a systematic review of articles published between 2010 and 2024, focusing on experimental and observational studies addressing the efficacy of these compounds.

Keywords: *alzheimer's disease, lysine, neuroinflam-mation, neuroprotection, peptides.*

GJMR-A Classification: *NLMC: WT 155*

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Peptides and Lysine: New Therapeutic Frontiers in the Fight Against Alzheimer's Disease

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Abstract- **Alzheimer's Disease (AD) is a prevalent neurodegenerative condition, affecting millions of people globally, particularly in an aging population. It is characterized by the aggregation of beta-amyloid and tau proteins, leading to the progressive loss of cognitive functions. This study investigates the therapeutic potential of peptides and the amino acid lysine in modulating the pathological processes of AD. The methodology included a systematic review of articles published between 2010 and 2024, focusing on experimental and observational studies addressing the efficacy of these compounds. The results indicate that specific peptides can destabilize amyloid plaques, while lysine contributes to neuroprotection and the reduction of neuroinflammation. Despite the promising findings, the efficacy and safety in humans still require validation through robust clinical trials. The discussion emphasizes the importance of understanding the underlying molecular mechanisms and the need for new therapeutic interventions. It is concluded that, although peptides and lysine show significant potential, continued research is crucial to develop effective strategies for treating AD, aiming to improve the quality of life for patients.**

Keywords: alzheimer's disease, lysine, neuroinflammation, neuroprotection, peptides.

I. Introduction

Alzheimer's Disease (AD) is a progressive neurodegenerative disorder, currently without a cure, that predominantly affects elderly individuals (Alzheimer's Association, 2024). It is characterized by a progressive decline in memory and other cognitive functions, significantly impacting occupational and social abilities. Initially, AD impairs processes such as learning and information retrieval, leading to a gradual deterioration in the capacity to acquire new knowledge. As the disease progresses, there is a further worsening, culminating in the inability to preserve remote memories (Souza *et al.*, 2023).

Alzheimer's Disease (AD) is a complex condition whose causes are not yet fully understood, but it is believed to result from an interaction between genetic, environmental, and lifestyle factors. Genetic predisposition is significant, especially in cases with mutations in the APP, PSEN1, and PSEN2 genes, as well as the presence of the APOE-ε4 allele, which increases the risk of developing the disease. Environmental factors, such as exposure to pollutants and heavy metals, have also been linked to a higher risk of AD. Additionally, lifestyle factors, including physical inactivity, poor diet, smoking, and chronic diseases like hypertension and diabetes, can contribute to the development of AD. Aging, the primary risk factor, is associated with chronic inflammation and the accumulation of neurotoxic proteins, which are directly related to the pathogenesis of AD (Scheltens *et al.*, 2021).

The neurodegenerative disease presented by Alzheimer's is the most prevalent in the world, affecting approximately 18 to 25 million people globally. It is the leading cause of dementia, accounting for between 50% and 56% of diagnosed cases (Souza; Santos; Silva, 2021). The impact of dementias extends beyond affected individuals, reaching their families and society as a whole, mainly due to the high socioeconomic burden these conditions impose (Neves, 2021). According to the World Health Organization (WHO), dementia is responsible for 11.9% of the years lived with disability caused by non-communicable diseases, with a global cost estimated at $604 billion in 2010 (Santos; Bessa; Xavier, 2020).

In Brazil, population aging has contributed to the increased prevalence of AD, highlighting the urgent need for more effective therapeutic strategies for managing this condition. Until recently, therapeutic approaches focused on symptomatic relief. Cholinesterase inhibitors, such as donepezil and rivastigmine, were widely used to improve cognitive function, although without significant effect on disease progression. However, recent advances in understanding the pathophysiological mechanisms of AD have driven the development of innovative therapies aimed not only at symptom relief but also at modifying the course of the disease (Bretas, 2023).

Currently, the use of peptides and lysine has been explored as a promising approach in the treatment of AD, due to their potential to modulate pathological processes associated with the disease. Synthetic peptides have shown the ability to interfere with beta-amyloid aggregation, one of the main markers of AD, promoting its destabilization and preventing the formation of neurotoxic amyloid plaques. On the other hand, lysine, an essential amino acid, has shown beneficial effects in controlling neuroinflammation and

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inhibiting the formation of cross-links in beta-amyloid and tau proteins. These mechanisms may contribute to reducing the accumulation of protein aggregates in the brain and preserving neuronal function (Singh *et al.*, 2023).

Lysine, an essential amino acid indispensable for protein synthesis and metabolic processes, is not produced by the human body and is obtained exclusively through diet. Peptides, on the other hand, are short chains of amino acids that play crucial biological roles, such as cellular signaling and the regulation of various physiological activities. In the context of Alzheimer's disease (AD), lysine and specific peptides have garnered attention for their potential in modulating neurodegenerative processes. Studies suggest that lysine may interfere with the aggregation of pathological proteins, such as the beta-amyloid peptide, while bioactive peptides demonstrate the ability to mitigate neuroinflammation, promote synaptic plasticity, and enhance cognitive functions (Yu *et al.*, 2021; Fonseca-Gomes *et al.*, 2024).

In this context, these advances suggest that lysine-based compounds and peptides may be promising in future therapeutic approaches for this debilitating condition. The progress in understanding the molecular mechanisms of AD has opened new therapeutic possibilities, with peptides and lysine standing out for their potential to modify the course of the disease. Despite significant advances, the search for more effective interventions remains a crucial challenge for medicine. Thus, exploring these approaches represents not only a scientific promise but also an essential step to address the growing prevalence and impact of AD in an aging global population.

Thus, this study aims to provide a comprehensive overview of AD, highlighting the urgent need for more effective therapeutic strategies. Additionally, it seeks to demonstrate the innovative therapeutic potential of peptides and lysine, emphasizing their ability to modulate pathological processes of AD, such as the aggregation of beta-amyloid and tau proteins, and their promising properties in controlling neuroinflammation.

II. Materials and Methods

The present study is a systematic review of a qualitative nature, conducted following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement. The studies were independently selected by three reviewers from the databases: PubMED, Cochrane, Scopus, LILACS, and SciELO. The controlled descriptors of Medical Subject Headings (MeSH) and Health Sciences Descriptors (DeCS) were standardized using the terms: “Peptides”, “Lysine”, “Treatment”, "Alzheimer Disease", combined using the Boolean operator “AND”.

The central question of the article was developed according to the PICO strategy (Table 1), in which the eligible components of the study were defined as follows: population (P): Patients diagnosed with Alzheimer's Disease; intervention (I): The use of peptides and the amino acid lysine as a therapeutic approach for the treatment of Alzheimer's Disease; comparison (C): Patients diagnosed with Alzheimer's disease who do not use peptides and the amino acid lysine as a therapeutic approach; outcome (O): Peptides and lysine assisting in the inhibition of protein aggregation, possessing neuroprotective properties, antioxidant and anti-inflammatory effects, in addition to improving cognitive function. In finalizing the method, the guiding question for the study was formed: "What is the impact of using peptides and the amino acid lysine as a therapeutic approach for Alzheimer's Disease?", which will be answered in the results and discussion of the article.

The inclusion criteria established were original articles, experimental and observational studies available in full text, those that addressed peptide therapy and the amino acid lysine in the treatment of Alzheimer's Disease, conducted in animals and humans, available for free, published between 2010 and 2024, and those in Portuguese and English. The search for articles was conducted in October 2024. The exclusion criteria were incomplete articles, duplicates, and those that did not fit within the following guiding question of the study defined by the PICO strategy.

The selection for identifying relevant studies was carried out in three stages: first, the article titles were examined to determine if they were aligned with the topic of interest. Next, the abstracts of the articles that passed the initial screening were read to verify if they met the inclusion criteria. Finally, the full texts of the selected articles were thoroughly reviewed to ensure they truly met all the established criteria for the research. The documents were organized using the Mendeley Reference Manager tool. Additionally, in cases of disagreement about inclusion, the studies were excluded. To assess the quality of the selected articles, the Grading of Recommendations Assessment, Development and Evaluation (GRADE) tool was used. This information was organized in a chart and subsequently discussed.

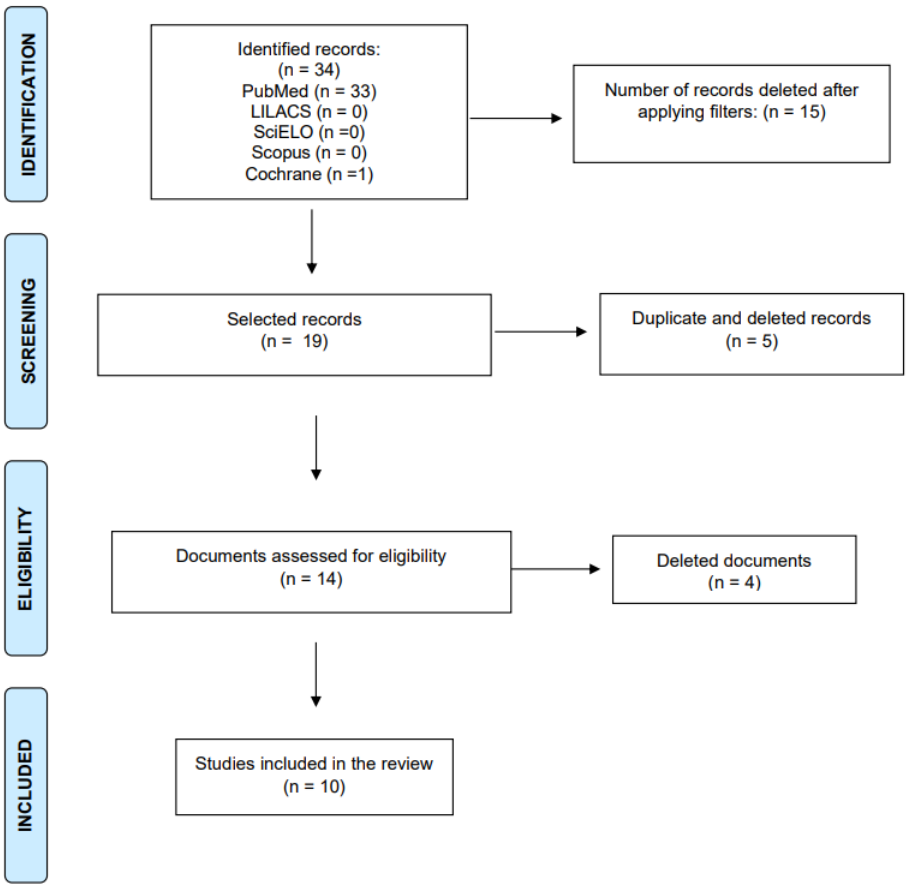
Thirty-four documents were found with the keywords, of which 15 did not meet the inclusion criteria of the study. After verifying duplicates, selecting titles and abstracts for reading, 5 more were excluded. Of the remaining 14 records, 4 were not eligible after full reading, totaling 10 selected articles (Table 2).

Table 1: Description of the PICO strategy to formulate the guiding research question: "What is the impact of using peptides and the amino acid lysine as a therapy for Alzheimer's Disease?"

Acrônimo	Definição	Descrição
P	Patients	Patients diagnosed with Alzheimer's Disease.
I	Intervention	The use of peptides and the amino acid lysine as a therapy for the treatment of Alzheimer's Disease.
C	Controls	Patients diagnosed with Alzheimer's disease who do not use peptides and the amino acid lysine as therapy.
O	Outcome	Peptides and lysine assist in inhibiting protein aggregation, possessing neuroprotective properties, antioxidant and anti-inflammatory effects, as well as improving cognitive function.

Source: Prepared by the authors (2024)

Table 2: PRISMA Flowchart



Source: Prepared by the authors (2024

III. Results

Out of the total of 10 articles analyzed, as shown in Table 3, the highest frequency of publication occurred in 2022 (n = 4), where "n" is the number of articles that meet the selected criteria, indicating a recent growing interest in the topic discussed. Regarding the Qualis classification of the journals in the sample, all 10 studies are allocated between the excellence ranges A1 to A3, according to the CAPES evaluation, reflecting the scientific relevance and high editorial quality of the publications. In terms of methodological approach, the majority of the articles used experiments as a basis for theoretical foundation and hypothesis testing (n = 9), demonstrating a preference for empirical methods to strengthen the evidence presented. Additionally, one study opted for a theoretical approach, contributing an analytical and integrative perspective on the available data.

Table 3: Studies Analyzing the Impact of using Peptides and the Amino Acid Lysine as Therapeutics for Alzheimer's Disease

ID	Autoria/Ano	Periódico (Qualis)	Métodos	Objetivos	Resultados
01	Pan *et al.* (2022)	Cell Metabolism **(A1)**	Experimental	Understanding how a positive feedback loop involving histone lactylation and PKM2 activation in microglia contributes to disease progression.	The enzyme PKM2 is elevated in microglia near β-amyloid plaques in Alzheimer's models, promoting histone lactylation (H4K12la) and activation of glycolytic genes, which exacerbates neuroinflammation. Inhibition of PKM2 reduces lactate, glycolytic genes, IL-6, TNF-α and may improve cognitive function, suggesting a promising therapeutic target.
02	Bai *et al.* (2022)	Cell Reports **(A1)**	Experimental	Investigate how SIRT2 modulates the acetylation of amyloid precursor protein (APP) and its impact on cognitive function and the pathology of Alzheimer's disease (AD) in APP/PS1 transgenic mice.	SIRT2 inhibition leads to an increase in the acetylation of amyloid precursor protein (APP) at lysines K132 and K134, resulting in greater production of the neuroprotective peptide sAPPa and promoting non-amyloidogenic processing of APP. Furthermore, SIRT2-deficient APP/PS1 mice showed significant improvements in cognitive function, evidenced by superior performance in spatial learning tests and a reduction in amyloid plaque burden in the brain, suggesting that modulation of APP acetylation by SIRT2 may be a promising therapeutic strategy for Alzheimer's disease.
03	Li *et al.* (2022)	Journal of Biological Chemistry **(A1)**	Case-control	Investigate the impact of TFEB acetylation on lysosomal biogenesis and β-amyloid (Aβ) clearance in APP/PS1 mice, analyzing the effect of Trichostatin A (TSA) on TFEB acetylation, its nuclear translocation, reduction of Aβ plaques, and cognitive improvements, aiming at new therapies for neurodegenerative diseases.	Treatment with Trichostatin A (TSA) in APP/PS1 mice reduced β-amyloid (Aβ) plaques by 62.8% in the cortex and 71.3% in the hippocampus, increased the expression of genes related to lysosomal biogenesis and autophagy, and improved learning and memory in behavioral tests. The results suggest that HDAC inhibition and TFEB acetylation may be promising strategies for treating Alzheimer's and neurodegenerative diseases.
04	Yu *et al.* (2021)	Journal of the American Society for Mass Spectrometry **(A2)**	Retrospective Experimental	Identify structural changes, post-translational modifications, and molecular interactions that influence lysine accessibility, elucidating the pathological mechanisms of the disease and its implications on brain function.	Alterations in lysine accessibility were identified in 17% of the proteome associated with Alzheimer's disease, identifying differentially exposed peptides in tau proteins and RNA splicing complexes, markers of the pathology. The native TMT methodology quantified changes in the structure of proteins related to transcription, mitochondrial, and synaptic functions. The

					results indicate that these alterations may be associated with post-translational modifications and protein aggregate formation, contributing to understanding the disease's molecular mechanisms.
05	Fonseca-Gomes *et al.* (2024)	Molecular Therapy **(A1)**	Experimental	Evaluate the efficacy and safety of the peptide TAT-TrkB as a therapy for Alzheimer's disease (AD), aiming to restore the function of BDNF and its receptor TrkB.	The peptide TAT-TrkB prevented the loss of rapid synaptic functions of BDNF induced by beta-amyloid (Ab) and restored long-term potentiation (LTP) in the hippocampus, suggesting the reactivation of TrkB-FL signaling. Additionally, TAT-TrkB prevented the excessive accumulation of the TrkB-ICD fragment, associated with dendritic spine loss and neuronal hyperactivity, and reduced the pathology of hyperphosphorylated tau, linked to deficits in neurogenesis and cognitive function. These results suggest that TAT-TrkB has potential as a disease-modifying agent, with the ability to prevent and reverse cognitive deficits in Alzheimer's patients.
06	Long *et al.* (2024)	Pharmacological Research **(A1)**	Experimental	Investigate the role of Kallistatin in cognitive function and glutamate homeostasis, focusing on transgenic mice (KAL-TG).	Transgenic mice for Kallistatin (KAL-TG) exhibited cognitive deficits in tests such as the Morris water maze and the Y-maze. They showed elevated basal glutamate levels and increased frequency of miniature excitatory postsynaptic currents (mEPSCs) in the CA1 region of the hippocampus, indicating dysfunction in glutamate homeostasis. The expression of glutamine synthetase (GS) in hippocampal astrocytes was reduced, while the EAAT2 transporter remained unchanged. Kallistatin promoted the degradation of GS through a proteasome-mediated mechanism involving acetylation and ubiquitination of the protein. Fenofibrate improved memory in KAL-TG mice, suggesting therapeutic potential against the effects of elevated Kallistatin.
07	Puris *et al.* (2021)	Scientific Reports **(A1)**	Case-control	To explore the effects of LPS-induced systemic inflammation on the plasma and brain metabolome and lipidome in APdE9 transgenic mice, a model of Alzheimer's disease.	The administration of LPS in transgenic APdE9 mice induced significant changes in the brain metabolome and lipidome, particularly in the cysteine and methionine metabolism pathways, arginine and proline, and fatty acids. These changes, more pronounced in LPS-treated APdE9 mice, indicate that systemic inflammation

					accelerates biochemical disturbances linked to Alzheimer's. In contrast, wild-type mice showed minimal changes, suggesting that inflammation impacts Alzheimer's models more than healthy organisms, reinforcing the role of infections in the metabolic worsening of the disease.
08	Song *et al.* (2023)	The Journal of Clinical Investigation **(A1)**	Prospective Experimental Study	Investigate the impact of tau protein acetylation at lysine 280 on pathological tau aggregation and the progression of tauopathies.	The monoclonal antibody Y01 has proven effective in preventing the progression of tauopathy induced by tau acetylated at lysine 280, significantly reducing tau aggregation and cell death in cell and mouse models. The results suggest that Y01 can protect neurons from the characteristic dysfunction of tauopathies, highlighting the importance of understanding tau modifications to develop specific therapies against neurodegenerative diseases such as Alzheimer's.
09	Rubey (2010)	Neuropsychiatric Disease and Treatment **(A3)**	Literature Review	Explore the hypothesis that lysine supplementation can prevent or delay the development of Alzheimer's disease (AD), particularly in relation to the reactivation of the herpes simplex virus type 1 (HSV-1), which has been implicated in the pathogenesis of AD.	Data indicate that HSV-1 is present in 90% of the brains of elderly individuals, including those with AD, and that its replication can be inhibited in environments rich in lysine and poor in arginine. It is suggested that lysine-rich diets, such as the Mediterranean diet, may be related to a lower risk of AD. Although definitive prospective studies are lacking, lysine supplementation is presented as a possible safe and economical strategy to prevent or mitigate AD, highlighting the need for future research to validate this hypothesis.
10	Bellver-Sanchis *et al.* (2022)	ChemMedChem **(A1)**	Experimental	Identifying new inhibitors of G9a, a lysine methyltransferase essential for the repression of genes linked to learning and memory, with the potential to treat neurodegenerative diseases.	The new G9a inhibitors demonstrated efficacy in reducing levels of the repressive marker H3K9me2, similar to the positive control UNC0638, indicating that they target G9a activity. They also significantly reduced amyloid β aggregate deposition in the transgenic C. elegans model, with up to a 25% reduction observed with UNC0638. Some compounds exhibited promising pharmacokinetic properties, although with lower blood-brain barrier permeability compared to UNC0638, possibly due to lower lipophilicity. These results highlight the potential of G9a inhibitors as therapeutic candidates for Alzheimer's.

Source: Prepared by the authors based on data obtained throughout the study (2024)

IV. Discussion

The use of peptides and the amino acid lysine as therapeutic strategies for Alzheimer's Disease (AD) has gained prominence due to their potential in modulating molecular mechanisms associated with the pathology. Studies suggest that specific peptides can interfere with the aggregation of toxic proteins, such as beta-amyloid, preventing or reducing the formation of senile plaques characteristic of AD. Lysine, in turn, plays an important role in regulating protein metabolism and stabilizing cellular structures, potentially contributing to neuroprotection and the improvement of synapses affected by neurodegeneration. Although these compounds show promising results in experimental models, their efficacy and safety in humans still need to be confirmed by robust clinical trials (Zhao *et al.*, 2020).

Pan *et al.* (2022) investigated the lactylation of histone H4K12 in microglia of Alzheimer's models, elucidating how this epigenetic modification contributes to microglial dysfunction and disease progression. The research demonstrated that H4K12 lactylation promotes an increase in the transcription of glycolytic genes, establishing a cycle that intensifies neuroinflammation. Inhibition of pyruvate kinase M2 (PKM2) was identified as a promising strategy to restore microglial function and reduce Aβ peptide load, pointing to new therapeutic perspectives for the treatment of Alzheimer's disease.

Various lysine modifications in histones have been analyzed, highlighting lysine 5 in histone H4 (H4K5la), associated with the regulation of gene expression; lysine 8 in histone H4 (H4K8la), involved in transcriptional regulation; and lysine 12 in histone H4 (H4K12la), the main focus of the study due to its direct relation to microglial dysfunction in Alzheimer's. Other relevant modifications include lysine 18 in histone H3 (H3K18la), with potential influence on chromatin structure, and lysine 23 in histone H3 (H3K23la), associated with the regulation of gene expression (Pan *et al.*, 2022).

Lysines present in histones are common targets for epigenetic modifications, such as lactylation, which directly affect chromatin structure and transcriptional activity. Among these alterations, lactylation of lysine 12 on histone H4 (H4K12la) has been identified as a critical factor in stimulating the expression of glycolytic genes, contributing to the activation and subsequent microglial dysfunction in Alzheimer's disease. Understanding these modifications is essential for advancing the knowledge of gene regulation mechanisms and investigating the pathogenesis of the disease (Pan *et al.*, 2022).

Bai *et al.* (2022) investigated the acetylation of the amyloid precursor protein (APP) and its impact on Alzheimer's disease pathology, aiming to understand how this epigenetic modification influences APP processing and the production of amyloid peptides associated with the disease's development. For this, two specific peptides were analyzed: APP-K132-AC and APP-K134-AC.

The peptide AAP-K132-AC, with the sequence ac-SDALLVPDK(ac)CKFLHQERMD-NH2, represents APP with lysine at position 132 acetylated, a relevant modification for studying cellular interactions and the function of APP, especially in the context of Alzheimer's disease. This acetylation may alter the structure and biological activity of the protein (Bai *et al.*, 2022).).

Similarly, the peptide AAP-K134-AC, with the sequence ac-LVPDKCK(ac)FLHQERMD-NH2, presents the APP with lysine at position 134 acetylated, a modification that affects the processing of APP and the production of amyloid peptides. The acetylation of lysines at positions K132 and K134 modifies the structure and function of APP, impacting its processing and the formation of amyloid aggregates, critical factors in the progression of Alzheimer's disease (Bai *et al.*, 2022).

To analyze these modifications, various experimental techniques were utilized. Immunocytochemistry was employed to visualize the localization and colocalization of APP and SIRT2 in primary neurons. Western Blot allowed for the detection and quantification of APP acetylation and the levels of its cleavage products. Streptavidin Pull-Down assays quantified APP on the cell surface in N2a-sw cells, while mass spectrometry identified the acetylated lysine residues on APP. Finally, ELISA assays measured the levels of sAPPa and sAPPb in brain tissue lysates, providing a detailed analysis of the implications of APP acetylation in disease pathology (Bai *et al.*, 2022). These findings highlight the relevance of epigenetic modifications in the regulation of APP and in understanding the molecular mechanisms underlying Alzheimer's disease, contributing to the identification of potential therapeutic targets.

From this perspective, according to Li *et al.* (2022), treatment with Trichostatin A (TSA), an HDAC inhibitor used in APP/PS1 mice, a model of Alzheimer's disease, showed significant effects on both pathology and cognitive function. The functionality of TSA lies in its ability to increase the expression of genes related to lysosomal biogenesis and autophagy, helping to reduce the accumulation of β-amyloid, one of the main markers of Alzheimer's Disease.

With this, a substantial reduction of β-amyloid (Aβ) plaques was observed, with decreases of 62.8% in the cortex and 71.3% in the hippocampus compared to vehicle-treated mice (saline) as part of the control group. Additionally, TSA increased the expression of genes associated with lysosomal biogenesis and autophagy, highlighting the crucial role of transcription factor EB (TFEB) acetylation in the activation of these processes (Li *et al.*, 2022).

In the context of cognitive function, mice treated with TSA showed significant improvements in learning

and memory tests, such as the Morris Water Maze, exhibiting less time to locate the platform and a higher frequency of crossings in the platform area compared to controls. The study also emphasized the importance of TFEB acetylation for its nuclear translocation and activation, highlighting the relevance of acetylation regulation in lysosomal biogenesis. These findings suggest that HDAC inhibition and the promotion of TFEB acetylation may constitute promising therapeutic strategies for Alzheimer's disease and other neurodegenerative diseases (Li *et al.*, 2022).

The study by Yu *et al.* (2021) on lysine accessibility and structural changes of proteins in brain samples from Alzheimer's patients identified 103 differentially exposed (DE) peptides, originating from 97 human proteins, with most being more abundant in the Alzheimer's samples. These data indicate an increase in lysine accessibility in proteins associated with neurofibrillary tangles and RNA splicing dysfunctions, hallmark features of the studied pathology.

Yu *et al.* (2021) investigated structural changes in proteins associated with Alzheimer's disease (AD), a condition characterized by protein misfolding and aggregation. The study aimed to understand how the lysine accessibility in protein peptides, such as tau and RNA splicing components, influences the disease pathology. A total of 15,370 peptides were identified, including those derived from tau proteins and 10 RNA splicing proteins, selected due to their relevance to cellular function and AD progression.

These peptides are crucial for understanding protein misfolding and RNA splicing dysfunction, which are central characteristics of the disease, and they can support the development of therapeutic strategies. To achieve this, the proteins were extracted under native conditions and subjected to Tandem Mass Tag (TMT) labeling, trypsin digestion, and analysis by liquid chromatography and mass spectrometry LC/LC-MS/MS (Yu *et al.*, 2021).

The large-scale analysis of lysine accessibility using TMT labeling revealed an increase in lysine accessibility in 9 out of 10 RNA splicing proteins in AD brain samples, indicating greater exposure of these regions, possibly related to misfolding and RNA splicing dysfunction. On the other hand, in the tau protein, a decrease in lysine accessibility was observed, corroborating its aggregation and misfolding, which have already been established as pathological features of AD (Yu *et al.*, 2021).

Alterations in lysine accessibility were also detected in proteins involved in mitochondrial and synaptic functions, suggesting that these structural changes affect multiple cellular processes and contribute to disease progression. These variations in accessibility reflect conformational changes and molecular interactions critical for understanding the underlying mechanisms of AD pathology, offering insights for new therapeutic approaches (Yu *et al.*, 2021).

Fonseca-Gomes *et al.* (2024) investigated synaptic dysfunction associated with Alzheimer's disease (AD), focusing on the cleavage of TrkB receptors. The study assessed the efficacy of TAT-TrkB peptides, a peptide that combines the TAT domain with the TrkB receptor sequence, in preventing BDNF receptor cleavage and restoring synaptic physiology in murine models of Alzheimer's, using cell-permeable peptides.

TAT-TrkB peptides were selected due to their ability to cross cell membranes and restore TrkB receptor function, which is compromised in AD. These peptides have been shown to prevent TrkB cleavage, promote BDNF signaling, and enhance synaptic plasticity, factors that can mitigate the cognitive deficits characteristic of the disease. The lysine in the TAT-TrkB peptide sequence played a key role, acting as a positive residue that facilitates interaction with cell membranes. This positive charge allowed overcoming the lipid barrier of the membrane, enabling the peptide's cellular translocation. Additionally, lysine contributed to the stability and solubility of the peptide in solution, enhancing its functionality (Fonseca-Gomes *et al.*, 2024).

The experimental protocol included the administration of TAT-TrkB in 5XFAD transgenic mice, followed by assessments of synaptic plasticity, analysis of TrkB cleavage, and measurements of cognitive performance. This approach allowed for the examination of the peptide's impact on preventing receptor cleavage and restoring synaptic function, contributing to the understanding of the underlying molecular mechanisms in AD and the development of promising therapeutic interventions (Fonseca-Gomes *et al.*, 2024).

Long *et al.* (2024) investigated the relationship between glutamate homeostasis and cognitive function in Alzheimer's models, with a focus on the dysfunction of the glutamatergic system in neurodegeneration and disease progression. The study examined the role of Kallistatin in glutamine synthesis, glutamate homeostasis, and its influence on cognitive function in transgenic mice (KAL-TG) that reproduce characteristics of Alzheimer's disease.

The analyzed peptides included Kallistatin, hydrocortisone, and fenofibrate. Kallistatin was the primary focus, while hydrocortisone and fenofibrate were used as complementary therapeutic agents. Glutamate was investigated due to its relevance as a central excitatory neurotransmitter in the nervous system. The research explored how dysfunction in glutamate homeostasis, often associated with excitotoxicity, contributes to cognitive decline in Alzheimer's models. The potential of Kallistatin to regulate glutamate levels and protect against its toxicity,

promoting improvements in cognitive function, was also evaluated (Long *et al.*, 2024).

The results demonstrated that Kallistatin can reduce glutamate toxicity, improve glutamine synthesis, and protect cognitive function. Hydrocortisone and fenofibrate also showed efficacy in mitigating the effects of neurodegeneration, with a positive impact on cognition (Long *et al.*, 2024).

Experiments were conducted on KAL-TG mice, subjected to behavioral tests such as the Morris water maze and the Y-maze for cognitive function assessment. Blood samples were collected for analysis of Kallistatin and glutamate levels, while the expression of proteins related to glutamine synthesis was evaluated in brain tissue (Long *et al.*, 2024).

The findings indicated that the regulation of Kallistatin is associated with improved glutamate homeostasis and the preservation of cognitive function in transgenic mice. Furthermore, treatments with hydrocortisone and fenofibrate demonstrated therapeutic potential for reducing the effects of neurodegeneration, suggesting that Kallistatin is a promising target for interventions in the treatment of Alzheimer's disease (Long *et al.*, 2024).

The results of the study conducted by Puris *et al.* (2021) on the effects of systemic inflammation in APdE9 transgenic mice demonstrated several significant alterations. The analyses revealed modifications in the levels of lipids in the cortex and hippocampus of mice treated with lipopolysaccharide (LPS). Specifically, a reduction was observed in certain phospholipids, such as PE ae C40:7 and PC aa C35:3/PE aa C38:3, while others, including PC ae C36:6 and PC ae C36:5, showed an increase in levels.

It was found that Aβ deposition was associated with the degradation of white matter, indicating that the molecular mechanisms involved in these metabolic and lipid alterations have complex and cell-specific characteristics. The statistical analysis in the study was conducted rigorously, using t-tests and ANOVA to evaluate the differences in cytokine and metabolite levels between the experimental groups. Bonferroni correction was applied to ensure statistical significance (Puris *et al.*, 2021).

The most altered biochemical pathways were identified using the pathway analysis module of MetaboAnalyst 4.0, allowing the comparison of the main characteristics of the metabolites analyzed. These results highlight the relevance of investigating metabolic changes in the context of Alzheimer's disease and the potential impact of systemic inflammation on these dynamics (Puris *et al.*, 2021).

Song et al. (2023) in their study demonstrated that the monoclonal antibody Y01 has a high specific affinity for the acetylated residue K280 of the tau protein, with the ability to inhibit tau aggregation induced by acetylation. Fluorescence assays using thioflavin T (ThT) showed that the addition of Y01 significantly reduced the aggregation of tau treated with the p300 enzyme in a concentration-dependent manner.

The modification of lysine 280 (K280), carried out to investigate its role in tau protein acetylation and subsequent aggregation, showed that by substituting K280 with alanine (K280A), researchers were able to assess how this alteration affects tau release and toxicity, as well as to better understand the contribution of K280 acetylation to the progression of tauopathies. The monoclonal antibody Y01, effective in detecting the tau-acK280 residue in brain tissue samples from P301L transgenic mice and human cerebrospinal fluid, revealed an interaction through hydrogen bonds and electrostatic complementarities between the antibody and tau protein residues, indicating its clinical potential in the neutralization and removal of pathological protein aggregates (Song *et al.*, 2023).

Rubey (2010) presents in his study highly relevant results about the relationship between herpes simplex virus type 1 (HSV-1) and Alzheimer's disease (AD), as well as the potential of lysine supplementation. HSV-1 DNA was detected in a high percentage (90%) of the brains of elderly individuals, including those diagnosed with AD, indicating that the virus can persist in the brain for long periods and reactivate itself, contributing to the pathogenesis of the disease.

Lysine is proposed as a potential inhibitor of HSV-1 activation, as diets high in lysine and low in arginine can suppress viral replication. Furthermore, the Mediterranean diet, characterized by high levels of lysine and low levels of arginine, may be associated with a lower prevalence of AD. This hypothesis is supported by studies indicating a reduced risk of AD in individuals who regularly consume fish, a food with a high lysine-to-arginine ratio (Rubey, 2010).

Investigations conducted by Rubey in 2010 revealed that a rural community in India exhibits significantly reduced rates of Alzheimer's Disease (AD) incidence compared to other regions. This phenomenon may be linked to a diet rich in dairy products, characterized by a high lysine to arginine ratio. Lysine, in particular, might play a crucial role in preventing the formation of amyloid plaques and neurofibrillary tangles, which are associated with AD, by inhibiting the activity of herpes simplex virus type 1 (HSV-1) in the brain. These findings suggest that exploring the interaction between diet, lysine, and HSV-1 activation could be a promising area for developing effective preventive strategies against AD.

Bellver-Sanchis *et al.* (2022) highlight that G9a inhibitors, identified through structure-based virtual screening, demonstrated significant efficacy in experimental models. On one hand, the compounds tested in this study exhibited promising ability to cross the blood-brain barrier; on the other hand, they were effective in improving age-related paralysis in a

transgenic model of Alzheimer's disease, specifically in the CL2006 lineage of Caenorhabditis elegans. Furthermore, these inhibitors had a positive impact on reducing amyloid-β aggregation, one of the main pathological markers associated with Alzheimer's disease.

G9a, also known as lysine methyltransferase or euchromatin histone-lysine N-methyltransferase 2 (EHMT2), is an enzyme whose main function is to add methyl groups to lysine 9 of histone H3 (H3K9), resulting in mono-methylation (H3K9me1) and di-methylation (H3K9me2). This methylation of H3K9 is an epigenetic mark associated with the repression of gene transcription, silencing genes by modifying the chromatin structure and making it less accessible to the transcription machinery. Furthermore, G9a plays a crucial role in regulating gene expression, affecting important biological processes such as development, cell differentiation, and stress response. Studied as a therapeutic target in various diseases, including cancer, psychiatric disorders, and neurodegenerative diseases like Alzheimer's Disease, G9a is associated with the repression of genes involved in learning and memory, contributing to cognitive impairment in these contexts.

Given the above, recent scientific investigations point to a wide range of promising therapeutic approaches for Alzheimer's disease, encompassing dietary interventions and peptide-based strategies to the use of enzyme inhibitors and monoclonal antibodies. These strategies aim not only to mitigate the structural and functional damage associated with the pathology but also to act on key processes such as toxic protein aggregation, neuroinflammation, and metabolic dysfunction. Although results in experimental models are encouraging, more robust research and large-scale clinical trials are still necessary to validate the efficacy and safety of these approaches in humans. Thus, advancing the understanding of the molecular mechanisms underlying Alzheimer's disease and the development of targeted therapeutic interventions may, in the future, transform the treatment landscape of this condition, bringing significant benefits to patients and caregivers.

V. Conclusions

Research on peptides and the amino acid lysine as therapies for Alzheimer's Disease reveals significant potential in modulating pathological processes associated with the disease. Peptides, especially those that act on beta-amyloid aggregation, demonstrate the ability to destabilize neurotoxic amyloid plaques. In turn, lysine plays a crucial role in regulating protein metabolism and cell stabilization, promoting neuroprotection and synaptic recovery. These substances not only reduce the accumulation of protein aggregates but also control neuroinflammation, a determining factor in the progression of the disease.

Although the results are promising, further studies are necessary to validate the efficacy and safety of using peptides and lysine in humans. Rigorous clinical trials are essential to confirm the therapeutic benefits and deepen the understanding of the mechanisms of action. Moreover, the continuation of research is crucial to elucidate molecular interactions and develop effective interventions that improve patients' quality of life.

Furthermore, the systematic literature review highlights the growing evidence that these interventions can inhibit protein aggregation and exhibit neuroprotective, antioxidant, and anti-inflammatory properties. This suggests that the use of peptides and lysine may improve cognitive function in patients with the disease.

However, it is important to recognize the limitations of this study, such as the variability of the methods in the reviewed articles and the predominance of studies in animal models, which may limit the generalizability of the results. For future research, it is recommended to conduct controlled clinical trials and investigations into the molecular mechanisms underlying these therapeutic effects.

The importance of the findings of this study lies in the possibility of developing new therapeutic approaches, significantly contributing to the management of Alzheimer's Disease. The identification of therapeutic targets, such as the inhibition of PKM2 and the modulation of APP acetylation, opens new perspectives for interventions that may alter the course of the disease. Therefore, the formulation of public policies focused on the treatment of Alzheimer's Disease, which affects millions of people globally, should be encouraged.

Therefore, the search for new therapies is urgent, and peptides and lysine may represent a valuable contribution in this context. This work emphasizes the importance of continuing the investigation into the role of these compounds in the treatment of Alzheimer's Disease, highlighting the need for a collaborative effort among researchers, clinicians, and policymakers to transform discoveries into effective practices that benefit patients with this neurodegenerative disease.

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Choice of the main keywords is the first tool of writing a research paper. Research paper writing is an art. Keyword search should be as strategic as possible.

One should start brainstorming lists of potential keywords before even beginning searching. Think about the most important concepts related to research work. Ask, “What words would a source have to include to be truly valuable in a research paper?” Then consider synonyms for the important words.

It may take the discovery of only one important paper to steer in the right keyword direction because, in most databases, the keywords under which a research paper is abstracted are listed with the paper.

Numerical Methods

Numerical methods used should be transparent and, where appropriate, supported by references.

Abbreviations

Authors must list all the abbreviations used in the paper at the end of the paper or in a separate table before using them.

Formulas and equations

Authors are advised to submit any mathematical equation using either MathJax, KaTeX, or LaTeX, or in a very high-quality image.

Tables, Figures, and Figure Legends

Tables: Tables should be cautiously designed, uncrowned, and include only essential data. Each must have an Arabic number, e.g., Table 4, a self-explanatory caption, and be on a separate sheet. Authors must submit tables in an editable format and not as images. References to these tables (if any) must be mentioned accurately.

Figures

Figures are supposed to be submitted as separate files. Always include a citation in the text for each figure using Arabic numbers, e.g., Fig. 4. Artwork must be submitted online in vector electronic form or by emailing it.

Preparation of Eletronic Figures for Publication

Although low-quality images are sufficient for review purposes, print publication requires high-quality images to prevent the final product being blurred or fuzzy. Submit (possibly by e-mail) EPS (line art) or TIFF (halftone/ photographs) files only. MS PowerPoint and Word Graphics are unsuitable for printed pictures. Avoid using pixel-oriented software. Scans (TIFF only) should have a resolution of at least 350 dpi (halftone) or 700 to 1100 dpi (line drawings). Please give the data for figures in black and white or submit a Color Work Agreement form. EPS files must be saved with fonts embedded (and with a TIFF preview, if possible).

For scanned images, the scanning resolution at final image size ought to be as follows to ensure good reproduction: line art: >650 dpi; halftones (including gel photographs): >350 dpi; figures containing both halftone and line images: >650 dpi.

Color charges: Authors are advised to pay the full cost for the reproduction of their color artwork. Hence, please note that if there is color artwork in your manuscript when it is accepted for publication, we would require you to complete and return a Color Work Agreement form before your paper can be published. Also, you can email your editor to remove the color fee after acceptance of the paper.

Tips for writing a good quality Medical Research Paper

1. Choosing the topic: In most cases, the topic is selected by the interests of the author, but it can also be suggested by the guides. You can have several topics, and then judge which you are most comfortable with. This may be done by asking several questions of yourself, like "Will I be able to carry out a search in this area? Will I find all necessary resources to accomplish the search? Will I be able to find all information in this field area?" If the answer to this type of question is "yes," then you ought to choose that topic. In most cases, you may have to conduct surveys and visit several places. Also, you might have to do a lot of work to find all the rises and falls of the various data on that subject. Sometimes, detailed information plays a vital role, instead of short information. Evaluators are human: The first thing to remember is that evaluators are also human beings. They are not only meant for rejecting a paper. They are here to evaluate your paper. So present your best aspect.

2. Think like evaluators: If you are in confusion or getting demotivated because your paper may not be accepted by the evaluators, then think, and try to evaluate your paper like an evaluator. Try to understand what an evaluator wants in your research paper, and you will automatically have your answer. Make blueprints of paper: The outline is the plan or framework that will help you to arrange your thoughts. It will make your paper logical. But remember that all points of your outline must be related to the topic you have chosen.

3. Ask your guides: If you are having any difficulty with your research, then do not hesitate to share your difficulty with your guide (if you have one). They will surely help you out and resolve your doubts. If you can't clarify what exactly you require for your work, then ask your supervisor to help you with an alternative. He or she might also provide you with a list of essential readings.

4. Use of computer is recommended: As you are doing research in the field of medical research then this point is quite obvious. Use right software: Always use good quality software packages. If you are not capable of judging good software, then you can lose the quality of your paper unknowingly. There are various programs available to help you which you can get through the internet.

5. Use the internet for help: An excellent start for your paper is using Google. It is a wondrous search engine, where you can have your doubts resolved. You may also read some answers for the frequent question of how to write your research paper or find a model research paper. You can download books from the internet. If you have all the required books, place importance on reading, selecting, and analyzing the specified information. Then sketch out your research paper. Use big pictures: You may use encyclopedias like Wikipedia to get pictures with the best resolution. At Global Journals, you should strictly follow here.

6. Bookmarks are useful: When you read any book or magazine, you generally use bookmarks, right? It is a good habit which helps to not lose your continuity. You should always use bookmarks while searching on the internet also, which will make your search easier.

7. Revise what you wrote: When you write anything, always read it, summarize it, and then finalize it.

8. Make every effort: Make every effort to mention what you are going to write in your paper. That means always have a good start. Try to mention everything in the introduction—what is the need for a particular research paper. Polish your work with good writing skills and always give an evaluator what he wants. Make backups: When you are going to do any important thing like making a research paper, you should always have backup copies of it either on your computer or on paper. This protects you from losing any portion of your important data.

9. Produce good diagrams of your own: Always try to include good charts or diagrams in your paper to improve quality. Using several unnecessary diagrams will degrade the quality of your paper by creating a hodgepodge. So always try to include diagrams which were made by you to improve the readability of your paper. Use of direct quotes: When you do research relevant to literature, history, or current affairs, then use of quotes becomes essential, but if the study is relevant to science, use of quotes is not preferable.

10. Use proper verb tense: Use proper verb tenses in your paper. Use past tense to present those events that have happened. Use present tense to indicate events that are going on. Use future tense to indicate events that will happen in the future. Use of wrong tenses will confuse the evaluator. Avoid sentences that are incomplete.

11. Pick a good study spot: Always try to pick a spot for your research which is quiet. Not every spot is good for studying.

12. Know what you know: Always try to know what you know by making objectives, otherwise you will be confused and unable to achieve your target.

13. Use good grammar: Always use good grammar and words that will have a positive impact on the evaluator; use of good vocabulary does not mean using tough words which the evaluator has to find in a dictionary. Do not fragment sentences. Eliminate one-word sentences. Do not ever use a big word when a smaller one would suffice.

Verbs have to be in agreement with their subjects. In a research paper, do not start sentences with conjunctions or finish them with prepositions. When writing formally, it is advisable to never split an infinitive because someone will (wrongly) complain. Avoid clichés like a disease. Always shun irritating alliteration. Use language which is simple and straightforward. Put together a neat summary.

14. Arrangement of information: Each section of the main body should start with an opening sentence, and there should be a changeover at the end of the section. Give only valid and powerful arguments for your topic. You may also maintain your arguments with records.

15. Never start at the last minute: Always allow enough time for research work. Leaving everything to the last minute will degrade your paper and spoil your work.

16. Multitasking in research is not good: Doing several things at the same time is a bad habit in the case of research activity. Research is an area where everything has a particular time slot. Divide your research work into parts, and do a particular part in a particular time slot.

17. Never copy others' work: Never copy others' work and give it your name because if the evaluator has seen it anywhere, you will be in trouble. Take proper rest and food: No matter how many hours you spend on your research activity, if you are not taking care of your health, then all your efforts will have been in vain. For quality research, take proper rest and food.

18. Go to seminars: Attend seminars if the topic is relevant to your research area. Utilize all your resources.

19. Refresh your mind after intervals: Try to give your mind a rest by listening to soft music or sleeping in intervals. This will also improve your memory. Acquire colleagues: Always try to acquire colleagues. No matter how sharp you are, if you acquire colleagues, they can give you ideas which will be helpful to your research.

20. Think technically: Always think technically. If anything happens, search for its reasons, benefits, and demerits. Think and then print: When you go to print your paper, check that tables are not split, headings are not detached from their descriptions, and page sequence is maintained.

21. Adding unnecessary information: Do not add unnecessary information like "I have used MS Excel to draw graphs." Irrelevant and inappropriate material is superfluous. Foreign terminology and phrases are not apropos. One should never take a broad view. Analogy is like feathers on a snake. Use words properly, regardless of how others use them. Remove quotations. Puns are for kids, not grunt readers. Never oversimplify: When adding material to your research paper, never go for oversimplification; this will definitely irritate the evaluator. Be specific. Never use rhythmic redundancies. Contractions shouldn't be used in a research paper. Comparisons are as terrible as clichés. Give up ampersands, abbreviations, and so on. Remove commas that are not necessary. Parenthetical words should be between brackets or commas. Understatement is always the best way to put forward earth-shaking thoughts. Give a detailed literary review.

22. Report concluded results: Use concluded results. From raw data, filter the results, and then conclude your studies based on measurements and observations taken. An appropriate number of decimal places should be used. Parenthetical remarks are prohibited here. Proofread carefully at the final stage. At the end, give an outline to your arguments. Spot perspectives of further study of the subject. Justify your conclusion at the bottom sufficiently, which will probably include examples.

23. Upon conclusion: Once you have concluded your research, the next most important step is to present your findings. Presentation is extremely important as it is the definite medium though which your research is going to be in print for the rest of the crowd. Care should be taken to categorize your thoughts well and present them in a logical and neat manner. A good quality research paper format is essential because it serves to highlight your research paper and bring to light all necessary aspects of your research.

Informal Guidelines of Research Paper Writing

Key points to remember:

- Submit all work in its final form.
- Write your paper in the form which is presented in the guidelines using the template.
- Please note the criteria peer reviewers will use for grading the final paper.

Final points:

One purpose of organizing a research paper is to let people interpret your efforts selectively. The journal requires the following sections, submitted in the order listed, with each section starting on a new page:

The introduction: This will be compiled from reference matter and reflect the design processes or outline of basis that directed you to make a study. As you carry out the process of study, the method and process section will be constructed like that. The results segment will show related statistics in nearly sequential order and direct reviewers to similar intellectual paths throughout the data that you gathered to carry out your study.

The discussion section:

This will provide understanding of the data and projections as to the implications of the results. The use of good quality references throughout the paper will give the effort trustworthiness by representing an alertness to prior workings.

Writing a research paper is not an easy job, no matter how trouble-free the actual research or concept. Practice, excellent preparation, and controlled record-keeping are the only means to make straightforward progression.

General style:

Specific editorial column necessities for compliance of a manuscript will always take over from directions in these general guidelines.

To make a paper clear: Adhere to recommended page limits.

Mistakes to avoid:

- Insertion of a title at the foot of a page with subsequent text on the next page.
- Separating a table, chart, or figure—confine each to a single page.
- Submitting a manuscript with pages out of sequence.
- In every section of your document, use standard writing style, including articles ("a" and "the").
- Keep paying attention to the topic of the paper.
- Use paragraphs to split each significant point (excluding the abstract).
- Align the primary line of each section.
- Present your points in sound order.
- Use present tense to report well-accepted matters.
- Use past tense to describe specific results.
- Do not use familiar wording; don't address the reviewer directly. Don't use slang or superlatives.
- Avoid use of extra pictures—include only those figures essential to presenting results.

Title page:

Choose a revealing title. It should be short and include the name(s) and address(es) of all authors. It should not have acronyms or abbreviations or exceed two printed lines.

Abstract: This summary should be two hundred words or less. It should clearly and briefly explain the key findings reported in the manuscript and must have precise statistics. It should not have acronyms or abbreviations. It should be logical in itself. Do not cite references at this point.

An abstract is a brief, distinct paragraph summary of finished work or work in development. In a minute or less, a reviewer can be taught the foundation behind the study, common approaches to the problem, relevant results, and significant conclusions or new questions.

Write your summary when your paper is completed because how can you write the summary of anything which is not yet written? Wealth of terminology is very essential in abstract. Use comprehensive sentences, and do not sacrifice readability for brevity; you can maintain it succinctly by phrasing sentences so that they provide more than a lone rationale. The author can at this moment go straight to shortening the outcome. Sum up the study with the subsequent elements in any summary. Try to limit the initial two items to no more than one line each.

Reason for writing the article—theory, overall issue, purpose.

- Fundamental goal.
- To-the-point depiction of the research.
- Consequences, including definite statistics—if the consequences are quantitative in nature, account for this; results of any numerical analysis should be reported. Significant conclusions or questions that emerge from the research.

Approach:

- Single section and succinct.
- An outline of the job done is always written in past tense.
- Concentrate on shortening results—limit background information to a verdict or two.
- Exact spelling, clarity of sentences and phrases, and appropriate reporting of quantities (proper units, important statistics) are just as significant in an abstract as they are anywhere else.

Introduction:

The introduction should "introduce" the manuscript. The reviewer should be presented with sufficient background information to be capable of comprehending and calculating the purpose of your study without having to refer to other works. The basis for the study should be offered. Give the most important references, but avoid making a comprehensive appraisal of the topic. Describe the problem visibly. If the problem is not acknowledged in a logical, reasonable way, the reviewer will give no attention to your results. Speak in common terms about techniques used to explain the problem, if needed, but do not present any particulars about the protocols here.

The following approach can create a valuable beginning:

- Explain the value (significance) of the study.
- Defend the model—why did you employ this particular system or method? What is its compensation? Remark upon its appropriateness from an abstract point of view as well as pointing out sensible reasons for using it.
- Present a justification. State your particular theory(-ies) or aim(s), and describe the logic that led you to choose them.
- Briefly explain the study's tentative purpose and how it meets the declared objectives.

Approach:

Use past tense except for when referring to recognized facts. After all, the manuscript will be submitted after the entire job is done. Sort out your thoughts; manufacture one key point for every section. If you make the four points listed above, you will need at least four paragraphs. Present surrounding information only when it is necessary to support a situation. The reviewer does not desire to read everything you know about a topic. Shape the theory specifically—do not take a broad view.

As always, give awareness to spelling, simplicity, and correctness of sentences and phrases.

Procedures (methods and materials):

This part is supposed to be the easiest to carve if you have good skills. A soundly written procedures segment allows a capable scientist to replicate your results. Present precise information about your supplies. The suppliers and clarity of reagents can be helpful bits of information. Present methods in sequential order, but linked methodologies can be grouped as a segment. Be concise when relating the protocols. Attempt to give the least amount of information that would permit another capable scientist to replicate your outcome, but be cautious that vital information is integrated. The use of subheadings is suggested and ought to be synchronized with the results section.

When a technique is used that has been well-described in another section, mention the specific item describing the way, but draw the basic principle while stating the situation. The purpose is to show all particular resources and broad procedures so that another person may use some or all of the methods in one more study or referee the scientific value of your work. It is not to be a step-by-step report of the whole thing you did, nor is a methods section a set of orders.

Materials:

Materials may be reported in part of a section or else they may be recognized along with your measures.

Methods:

- Report the method and not the particulars of each process that engaged the same methodology.
- Describe the method entirely.
- To be succinct, present methods under headings dedicated to specific dealings or groups of measures.
- Simplify—detail how procedures were completed, not how they were performed on a particular day.
- If well-known procedures were used, account for the procedure by name, possibly with a reference, and that's all.

Approach:

It is embarrassing to use vigorous voice when documenting methods without using first person, which would focus the reviewer's interest on the researcher rather than the job. As a result, when writing up the methods, most authors use third person passive voice.

Use standard style in this and every other part of the paper—avoid familiar lists, and use full sentences.

What to keep away from:

- Resources and methods are not a set of information.
- Skip all descriptive information and surroundings—save it for the argument.
- Leave out information that is immaterial to a third party.

Results:

The principle of a results segment is to present and demonstrate your conclusion. Create this part as entirely objective details of the outcome, and save all understanding for the discussion.

The page length of this segment is set by the sum and types of data to be reported. Use statistics and tables, if suitable, to present consequences most efficiently.

You must clearly differentiate material which would usually be incorporated in a study editorial from any unprocessed data or additional appendix matter that would not be available. In fact, such matters should not be submitted at all except if requested by the instructor.

Content:

- Sum up your conclusions in text and demonstrate them, if suitable, with figures and tables.
- In the manuscript, explain each of your consequences, and point the reader to remarks that are most appropriate.
- Present a background, such as by describing the question that was addressed by creation of an exacting study.
- Explain results of control experiments and give remarks that are not accessible in a prescribed figure or table, if appropriate.
- Examine your data, then prepare the analyzed (transformed) data in the form of a figure (graph), table, or manuscript.

What to stay away from:

- Do not discuss or infer your outcome, report surrounding information, or try to explain anything.
- Do not include raw data or intermediate calculations in a research manuscript.
- Do not present similar data more than once.
- A manuscript should complement any figures or tables, not duplicate information.
- Never confuse figures with tables—there is a difference.

Approach:

As always, use past tense when you submit your results, and put the whole thing in a reasonable order.

Put figures and tables, appropriately numbered, in order at the end of the report.

If you desire, you may place your figures and tables properly within the text of your results section.

Figures and tables:

If you put figures and tables at the end of some details, make certain that they are visibly distinguished from any attached appendix materials, such as raw facts. Whatever the position, each table must be titled, numbered one after the other, and include a heading. All figures and tables must be divided from the text.

Discussion:

The discussion is expected to be the trickiest segment to write. A lot of papers submitted to the journal are discarded based on problems with the discussion. There is no rule for how long an argument should be.

Position your understanding of the outcome visibly to lead the reviewer through your conclusions, and then finish the paper with a summing up of the implications of the study. The purpose here is to offer an understanding of your results and support all of your conclusions, using facts from your research and generally accepted information, if suitable. The implication of results should be fully described.

Infer your data in the conversation in suitable depth. This means that when you clarify an observable fact, you must explain mechanisms that may account for the observation. If your results vary from your prospect, make clear why that may have happened. If your results agree, then explain the theory that the proof supported. It is never suitable to just state that the data approved the prospect, and let it drop at that. Make a decision as to whether each premise is supported or discarded or if you cannot make a conclusion with assurance. Do not just dismiss a study or part of a study as "uncertain."

Research papers are not acknowledged if the work is imperfect. Draw what conclusions you can based upon the results that you have, and take care of the study as a finished work.

- You may propose future guidelines, such as how an experiment might be personalized to accomplish a new idea.
- Give details of all of your remarks as much as possible, focusing on mechanisms.
- Make a decision as to whether the tentative design sufficiently addressed the theory and whether or not it was correctly restricted. Try to present substitute explanations if they are sensible alternatives.
- One piece of research will not counter an overall question, so maintain the large picture in mind. Where do you go next? The best studies unlock new avenues of study. What questions remain?
- Recommendations for detailed papers will offer supplementary suggestions.

Approach:

When you refer to information, differentiate data generated by your own studies from other available information. Present work done by specific persons (including you) in past tense.

Describe generally acknowledged facts and main beliefs in present tense.

The Administration Rules

Administration Rules to Be Strictly Followed before Submitting Your Research Paper to Global Journals Inc.

Please read the following rules and regulations carefully before submitting your research paper to Global Journals Inc. to avoid rejection.

Segment draft and final research paper: You have to strictly follow the template of a research paper, failing which your paper may get rejected. You are expected to write each part of the paper wholly on your own. The peer reviewers need to identify your own perspective of the concepts in your own terms. Please do not extract straight from any other source, and do not rephrase someone else's analysis. Do not allow anyone else to proofread your manuscript.

Written material: You may discuss this with your guides and key sources. Do not copy anyone else's paper, even if this is only imitation, otherwise it will be rejected on the grounds of plagiarism, which is illegal. Various methods to avoid plagiarism are strictly applied by us to every paper, and, if found guilty, you may be blacklisted, which could affect your career adversely. To guard yourself and others from possible illegal use, please do not permit anyone to use or even read your paper and file.

Criterion for Grading a Research Paper (Compilation) by Global Journals

Please note that following table is only a Grading of "Paper Compilation" and not on "Performed/Stated Research" whose grading solely depends on Individual Assigned Peer Reviewer and Editorial Board Member. These can be available only on request and after decision of Paper. This report will be the property of Global Journals.

Topics	Grades		
	A-B	**C-D**	**E-F**
Abstract	Clear and concise with appropriate content, Correct format. 200 words or below	Unclear summary and no specific data, Incorrect form Above 200 words	No specific data with ambiguous information Above 250 words
Introduction	Containing all background details with clear goal and appropriate details, flow specification, no grammar and spelling mistake, well organized sentence and paragraph, reference cited	Unclear and confusing data, appropriate format, grammar and spelling errors with unorganized matter	Out of place depth and content, hazy format
Methods and Procedures	Clear and to the point with well arranged paragraph, precision and accuracy of facts and figures, well organized subheads	Difficult to comprehend with embarrassed text, too much explanation but completed	Incorrect and unorganized structure with hazy meaning
Result	Well organized, Clear and specific, Correct units with precision, correct data, well structuring of paragraph, no grammar and spelling mistake	Complete and embarrassed text, difficult to comprehend	Irregular format with wrong facts and figures
Discussion	Well organized, meaningful specification, sound conclusion, logical and concise explanation, highly structured paragraph reference cited	Wordy, unclear conclusion, spurious	Conclusion is not cited, unorganized, difficult to comprehend
References	Complete and correct format, well organized	Beside the point, Incomplete	Wrong format and structuring

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