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EXPLORING THE LIPIDOMIC PROFILE: UNRAVELING THE POTENTIAL LINK BETWEEN LIPIDS AND MENTAL HEALTH DISORDERS

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Abstract

The ever-rising and prevailing level of brain diseases is of great concern and has been regarded as challenging to global health, contributing to increasing the global disease burden. Brain disorders have primarily affected cognition and neurological performance and, therefore, can affect an individual's personal and social life. Lipids are large organic molecules that significantly contribute to the progression of cardiovascular diseases. The eight different categories of lipids involved in the formation of the central nervous system include Fatty acyls, glycerophospholipids, glycerolipids, sphingolipids, prenol lipids, sterol lipids, polyketides, and saccharolipids. The lipids provide a source of energy in the form of triglycerides and form a variety of secondary messengers that provide their necessary precursors. These precursors may include arachidonic acid (ArAc), ceramide, docosahexaenoic acid (DHA), 1,2-diacylglycerol (DAG), lysophosphatidic acid, and phosphatidic acid. The normal physiological function of the brain is attributable to the overall normal function of lipid precursors. Any pathological deviations or injuries to the brain's neuronal structure make decisions for developing neurodegenerative disorders, mental diseases, CNS traumas, and stroke. A nonregulation in the metabolism of lipids underlies the development and progression of neurodegenerative disorders and neurological diseases. Inside the brain, amyloid-b plaques constitute the pathogenesis of the disease and lead to the atrophy of the neurotic tissues. Neurological disorders like Alzheimer's disease (A.D.), Parkinson's disease (P.D.), schizophrenia and bipolar disorders, Huntington's disease (H.D.), Multiple sclerosis, and depression are psychological issues and it is a severe medical problem that affects the person badly by affecting health, thinking, behavior, and mood.

Introduction

Lipids are large organic molecules that significantly contribute to the progression of cardiovascular diseases (Akoh & Lai, 2019; Tsoupras et al., 2019; Zeldin & Honn, 2019). Lipids also have a significant role in forming various biological structures, such as forming the lipid barrier and cell membrane of neuron (Fonteh et al., 2021; Trostchansky & Rubbo, 2019). Lipids are essential for brain structure

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formation and neuron physiology (Hajek & Salvi, 2019; Vernon et al., 2021). The lipid composition governs various brain functions such as perception, mood, and emotional behavior (Stubbs et al., 2019; Wallace, 2013). The eight different categories of lipids involved in the formation of the Central Nervous System (CNS) include Fatty acyls, glycerophospholipids, glycerolipids, sphingolipids, prenol lipids, sterol lipids, polyketides, and saccharolipids (Rodwell, 2022).

In the biological process, various functions of lipids involve the construction of a cell's lipid bilayer, which gives a cell structure and provides means for the function of proteins, providing a source of energy in the form of triglycerides and for a variety of secondary messenger provide their necessary precursors (Fonteh et al., 2021; Zeldin & Honn, 2019). These precursors may include arachidonic acid (ArAc), ceramide, docosahexaenoic acid (DHA), 1,2-diacylglycerol (DAG), lysophosphatidic acid, and phosphatidic acid (Trostchansky & Rubbo, 2019). The brain's normal physiological function is attributable to these compounds' overall normal function (Rodwell, 2022).

Any pathological deviations or injuries to the brain's neuronal structure make decisions for developing neurodegenerative disorders, mental diseases, CNS traumas, and stroke (DiPiro et al., 2023; Ebert et al., 2024; Fernando et al., 2019). Once any CNS-damaging diseases or injuries occur, there is no cure for the CNS system, thus contributing to poor quality of life (Fauci et al., 2025; Hajek & Salvi, 2019). Several neurological diseases demonstrate the pivotal role of lipids in the signaling and physiology of cells and tissues (Trostchansky & Rubbo, 2019; Zeldin & Honn, 2019). A nonregulation in the metabolism of lipids underlies the development and progression of neurodegenerative disorders and neurological diseases (Fernando et al., 2019; Wallace, 2013). An alteration or change in the normal metabolism of lipids plays a significant role in developing CNS injuries (Apigian, 2025; Ebert et al., 2024).

The definition of normal mental health can be put together as a state of being well in which every person can recognize their potential, can cope or face the usual tensions of an individual's life, can work fruitfully and productively, and is capable of contributing to their community (Stubbs et al., 2019; Vernon et al., 2021). Almost four fifty million individuals globally cannot enjoy this state of mental health (David, 2023; Wallace, 2013). It has been calculated that every one in four will face challenges regarding mental health at some stage of their life, leading to great suffering, financial, social, and personal losses, and physical disorders associated with poor mental health (Apigian, 2025; Fauci et al., 2025).

Establishing and recognizing the attributing risk factors and efficient treatment plans is a global priority (David, 2023; Stubbs et al., 2019). The human brain relies heavily on both micro and macronutrients when it comes to maintaining proper mental well-being showing the importance of the role of nutrition in mental health (Akoh & Lai, 2019; Tsoupras et al., 2019). More importantly, a subnormal level of polyunsaturated omega-3 fatty acids has become a risk factor for mental disorders and can be modified (Fonteh et al., 2021; Rodwell, 2022). Long-chain omega-3 Polyunsaturated fatty acid (PUFA) was discovered in the 1970s to be an essential component of brain tissues have been predicted to play crucial roles in the function and development of the brain (Zeldin & Honn, 2019).

Several mental disorders have been seen to be attributed to a deficient in the levels of these fatty acids, including mental retardation and developmental disorders in early stages of life, to bipolar disorders, depression, borderline personality disorder and schizophrenia, hostility, stress, and aggression in adults, and Alzheimer's disease, dementia and cognitive decline in middle age (DiPiro et al., 2023; Ebert et al., 2024; Fernando et al., 2019; Hajek & Salvi, 2019).

The ever-rising and prevailing level of brain diseases is of great concern (Fauci et al., 2025; Vernon et al., 2021). It has been regarded as challenging to global health and has also contributed to increasing the global disease burden (Stubbs et al., 2019; Wallace, 2013). Cognition and neurological performance have been primarily affected by brain disorders and, therefore, can affect an individual's personal and social life (Apigian, 2025; David, 2023;

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Trostchansky & Rubbo, 2019; Tsoupras et al., 2019).

Research Justification

1. **Emerging biomarker interest:** With the growing knowledge about the underlying molecular basis of mental health disorders, there is more interest in finding reliable and clinically relevant biomarkers. Cell membranes and signaling molecules contain lipids, which are important constituents of the neural compartment. Their potential as biomarkers is worth studying because it would bring useful information about the pathophysiology of mental health disorders.
2. **A whole-person perspective on mental health:** Mental illnesses are multi-dimensional and multi-layered, and in many cases, genetic, environmental, and biochemical factors interact in a complicated way. Conventional studies have more or less been based on neurotransmitters and genetics but a holistic view to include lipidomic profiles can provide a better insight to the mechanisms involved.
3. **The role of lipids in the brain:** Lipids are part of the brain structure and brain function and play a role in synaptic plasticity, neurotransmission, and neuroinflammation. A more comprehensive lipidomic study may reveal particular species or ratios of lipids that are correlated with mental health issues, which would inform the therapeutic focus.
4. **Diagnostic and prognostic potential:** Diagnostic and prognostic tools could be developed as a result of identifying lipidomic signatures of diverse mental health disorders. The tools may lead to early diagnosis, personalized treatment plan, and treatment response monitoring, which would lead to better patient outcomes.
5. **Drug development and treatment strategies:** Lipid metabolism is a process that can be manipulated and hence it is an excellent target of drug development. It may provide the path to the new therapeutic interventions, such as lipid-based treatment or lifestyle change based on the understanding of the association between lipidomic alterations with mental health.
6. **Translational implications:** Lipidomic profiling can potentially be used in primary and translational research. Basic research is able to clarify the biochemical foundation of mental illnesses, and translational research can help develop an application of the research in clinical practice.
7. **Precision psychiatry possible:** Precision psychiatry seeks to offer personalized treatment to patients according to their unique molecular patterns. Lipidomic profiling may help to build up a precision medicine strategy, as clinical workers can choose the most effective strategies to use in every patient.
8. **Contribution to the field:** Due to the very little knowledge of the lipidomic basis of mental health disorders, studies in the field may play a huge role towards the knowledge base of the field. It may result in the paradigm shift in mental health perception and create new possibilities to work in collaboration and interdisciplinary research.

Lipids and Mental Health Disorders: A Probable Relationship

Lipids may act as signaling molecules or neurotransmitters that contribute to developing mental health disorders (Akoh & Lai, 2019; Wallace, 2013; Zeldin & Honn, 2019). The role of lipids in the development and progression of mental disorders at various stages is influenced by environmental factors, nutrition, aging, and behavioral activity (Apigian, 2025; David, 2023; Stubbs et al., 2019). Neurological disorders like Alzheimer's disease (A.D.), Parkinson's disease (P.D.), schizophrenia and bipolar disorders, Huntington's disease (H.D.), Multiple sclerosis, and depression are psychological issues where lipids act as targets for understanding psychiatric disorders (Fauci et al., 2025; Hajek & Salvi, 2019; Vernon et al., 2021).

1. **Alzheimer's Disease (A.D.)**

Alzheimer is a progressive brain disorder and a prevalent type of dementia that affects regions of the brain that control cognition and memory (DiPiro et al., 2023; Ebert et al., 2024). Hence, AD is a human disorder that damages a person's potential to learn, memorize, communicate,

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reason, and carry out routine tasks (David, 2023; Fauci et al., 2025). A.D. is classified into two types: an early onset A.D. and a late onset A.D. (Fernando et al., 2019; Vernon et al., 2021). Early onset A.D. occurs in individuals younger than 65 years and vice versa. Early onset A.D. comprises only 5% to 10% of Alzheimer's diseases, while late onset is more common, with a 90 to 95% percentage. Biochemistry shows cholesterol to be of a pivotal role in the development of the disease (Akoh & Lai, 2019; Rodwell, 2022). Our plasma contains a very abundant form of apolipoprotein E (APOE) which acts as a carrier protein for transporting cholesterol in the brain and identifying the gene encoding for the APOE e4 allele as a significant risk factor for A.D. with evidence for the role of cholesterol in the development of the disease (Fonteh et al., 2021; Zeldin & Honn, 2019).

Studies have shown that too much production of the protein amyloid-b has subunits, Ab40 and Ab42, contributing to the development of A.D. Inside the brain, amyloid-b plaques constitute the pathogenesis of the disease and lead to the atrophy of the neurotic tissues (Hajek & Salvi, 2019; Trostchansky & Rubbo, 2019). Lipid and cholesterol synthesis is carried out by an enzyme HMG-CoA reductase, and it has been shown that Ab40 is involved in inhibiting this essential enzyme (Akoh & Lai, 2019; Rodwell, 2022). Ab42 has been shown to accelerate the neurodegeneration process as it enhances ceramide production by activating the (N-SMase) neutral sphingomyelinase (Fonteh et al., 2021; Zeldin & Honn, 2019). Based on this underlying mechanism, it can be assumed that a combination of Ab40 and Ab42 antagonists as well as a lipid-rich dietary regime, can be effective for the palliative treatment of A.D. (Tsoupras et al., 2019; Wallace, 2013).

Enhanced lipid peroxidation has been demonstrated in A.D. by various studies. Acrolein is formed as a result of this lipid peroxidation which is the strongest in all of the a, b-unsaturated aldehydes (Fernando et al., 2019; Trostchansky & Rubbo, 2019). Acrolein forms cyclic adducts by reacting with the four DNA bases, such as guanine, cytosine, adenine, and thymidine; acrolein deoxyguanosine is the major exocyclic adduct (DiPiro et al., 2023; Ebert et al., 2024). Reactive oxygen species (ROS) cause the cross-linking of the amyloid-b peptides, thus progressing the degenerative mechanism of A.D. (Apigian, 2025; Zeldin & Honn, 2019).

2. **Parkinson's Disease (P.D.)**

Substantia nigra (SN)is a basal ganglion present in the midbrain that contains dopaminergic neurons, which are degenerated in Parkinson's disease (P.D.), leading to rigidity, tremor, and bradykinesia (Ebert et al., 2024; Fauci et al., 2025). S.N. has been shown that Monoamine oxidase-B is hyperactivated, causing the fall in the level of dopamine in the brain (David, 2023; Rodwell, 2022). The process leads to lipid peroxidation and accumulation of ROS (Akoh & Lai, 2019; Trostchansky & Rubbo, 2019).

The activation of the phospholipases in substantia nigra is considered to be a responsible factor (Fonteh et al., 2021; Zeldin & Honn, 2019). The formation of small agglomerates of an a-synuclein protein called Lewy bodies has been associated with the development of P.D. (Fernando et al., 2019; Vernon et al., 2021). Apart from the lewy bodies associated with PUFA, and all the others remain in a soluble state in the brain (Tsoupras et al., 2019; Wallace, 2013). This insolubility of the PUFA-associated Lewy bodies makes them asymptomatic.

Stimulation of the oligomerization of a-synuclein by docosahexaenoic acid has been reported in studies (Akoh & Lai, 2019; Rodwell, 2022). Recently studies have demonstrated an elevated level of this fatty acid in P.D. patients compared to control groups showing that the fatty acid may contribute to the insoluble formation of a-synuclein aggregates which are asymptomatic (Hajek & Salvi, 2019; Stubbs et al., 2019). Hence DHA can enhance the quality of life of a P.D. patient.

Lipid peroxidation is essential in developing P.D. An 8-hydroxy-20 – deoxyguanosine, a guanine nucleotide damaged by the free radicles, is elevated in P.D. patients (DiPiro et al., 2023; Ebert et al., 2024). It is an essential biomarker for evaluating deoxyribonucleic acid (DNA) damage (David,

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2023; Fauci et al., 2025). Several other biomarkers of lipid peroxidation are raised in P.D. patients (Apigian, 2025; Fernando et al., 2019). Moreover, 4-hydroxy-2- nonenal has also been found to be raised in P.D. patients and is a product of arachidonic acid peroxidation (Trostchansky & Rubbo, 2019; Zeldin & Honn, 2019). The process indicates that P.D. is progressed by lipid peroxidation and accelerating dopamine metabolism.

3. **Schizophrenia and Bipolar Disorders**

Drugs blocking the dopamine receptors seem to improve the patient's symptoms of schizophrenia and indicate an enhanced dopamine-related function (David, 2023; Fauci et al., 2025). Compared to dopamine drugs, blocking the glutamate receptors causes an average person to develop symptoms of schizophrenia (DiPiro et al., 2023; Ebert et al., 2024). Schizophrenia is characterized by disturbed emotional reactions, thinking, social behavior, hallucinations, and delusions (Stubbs et al., 2019; Vernon et al., 2021). Recent studies on the neurological disturbances occurring in schizophrenia have primarily targeted the anomalies in the phospholipid metabolism, especially that of the increase in function of polylactic acid (PLA)degrading enzymes and a reduction in the function of the system which forms phospholipids from PUFAs (Fonteh et al., 2021; Rodwell, 2022). The two pivotal fatty acids in monoaminergic neurotransmission, synaptic function, and brain development include eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) (Akoh & Lai, 2019; Tsoupras et al., 2019). Fatty acids are already established to oxidize monoamines responsible for the progression of neurological disorders (Trostchansky & Rubbo, 2019; Zeldin & Honn, 2019). EPA and DHA contribute to inhibiting disease progression by increasing the neurotransmission mediated by monoamines (Fernando et al., 2019; Wallace, 2013).

Bipolar disorder, formerly called manic depression, is a mental health condition that causes extreme mood swings that include emotional highs (mania or hypomania) and lows (depression) (Apigian, 2025; Vernon et al., 2021). Symptoms of this disease include a significantly elevated mood called mania. They can also include episodes of depression (David, 2023; Fauci et al., 2025). Bipolar disorder is also known as bipolar disease or manic depression (DiPiro et al., 2023; Ebert et al., 2024). Researchers are learning that the brain structure and function of people with bipolar disorder may be different from the brain structure and function of people who do not have bipolar disorder or other psychiatric disorders (Hajek & Salvi, 2019; Stubbs et al., 2019). These chronic mental disorders affect the population and can notably interfere with an individual's everyday life.

4. **Huntington's Disease (H.D.)**

Cognitive decline, behavioral abnormalities, and involuntary movement characterize a neurological disorder, Huntington's disease (H.D.) (Ebert et al., 2024; Fernando et al., 2019). Research conducted on humans and animals revealed that disrupted cholesterol metabolism is an essential factor in the pathogenesis of H.D. (Akoh & Lai, 2019; Rodwell, 2022). Abnormality in lipid metabolism is associated with the specific action of mutants (Fonteh et al., 2021; Zeldin & Honn, 2019).

Huntington gene to sterol regulatory binding proteins generally causes a decline in cholesterol levels in affected brain areas (Tsoupras et al., 2019; Wallace, 2013). The other important factor contributing to H.D.'s pathophysiology is insulin resistance in low-weight patients and patients with a low body mass index (David, 2023; Fauci et al., 2025). Medications that combat the abnormal lipid milieu are proven beneficial for treating H.D. (Stubbs et al., 2019; Vernon et al., 2021).

5. **Multiple Sclerosis (M.S.)**

Multiple sclerosis (M.S.) is a neurodegenerative disorder characterized by an inflammatory demyelinating disease affecting the central nervous system (DiPiro et al., 2023; Ebert et al., 2024). In MS disease, the immune system attacks on myelin sheath of nerve cell fibers in the spinal cord and brain (Fonteh et al., 2021; Hajek & Salvi, 2019).

In MS, symptoms begin to be severe and disabling due to the disrupted communication between the brain and restring parts of the brain and the

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inability to write, speak and walk (Fauci et al., 2025; Rodwell, 2022). This disease is marked by the high level of ethane and pentane in urine (Akoh & Lai, 2019; Trostchansky & Rubbo, 2019). Both ethane and pentane lead to monounsaturated fatty acid degradation.

6. Depression

Major depressive disorder (MDD) is a psychological and severe medical problem that affects the person badly by acting on the person's thinking, behavior, and mood (Apigian, 2025; David, 2023). MDD individuals generally experience sadness or loss of interest in activities of daily living (Stubbs et al., 2019; Vernon et al., 2021). The individuals cannot perform their daily routine functions appropriately (Ebert et al., 2024; Fauci et al., 2025). Cholesterol, with its disrupted metabolism, causes major depressive disorder (Akoh & Lai, 2019; Rodwell, 2022). Cholesterol plays a vital role in regulating ion channels and membrane-bound proteins. Furthermore, it is required to form dendrites, synapses, and axons (Fonteh et al., 2021; Zeldin & Honn, 2019). It decreases synaptic plasticity and failed neurotransmission when impaired, leading to MDD (Fernando et al., 2019; Wallace, 2013). Cholesterol-rich diet is promising in treating MDD.

Lipid Biomarkers and Mental Disorders: Underlying Mechanisms

Lipid biomarker research has been an extensive success in various medical fields so far, but using biomarkers to diagnose and predict treatment responses for mental disorders is still a challenge (Trostchansky & Rubbo, 2019; Tsoupras et al., 2019). The eight classes of lipids derived from prokaryotic or eukaryotic sources and used as biomarkers for neurodegenerative diseases are Fatty acids and hydroxyl fatty acids, Glycerolipids, Glycerophospholipids, Sphingolipids, Sterol lipids, Sacchrolipids, Prenol lipids, and polyketides (Fonteh et al., 2021; Rodwell, 2022). They are involved in different biological processes that are biomarkers for cognitive diseases such as Alzheimer's disease (A.D.), Parkinson's disease (P.D.), schizophrenia and bipolar disorders, Huntington's disease (H.D.), Multiple sclerosis and depression (Fauci et al., 2025; Vernon et al., 2021).

Conclusion

The role of lipids in these mental disorders' pathogenesis can now be clearly understood. Especially lipid peroxidation can be regarded as a critical event in the pathological progression of mental diseases. The ever-rising and prevailing level of brain diseases is of great concern. It has been regarded as challenging to global health and increased global disease burden. Brain disorders have primarily affected cognition and neurological performance and, therefore, can affect an individual's personal and social life and family. Organic large molecules, lipids significantly contribute to the progression of cardiovascular diseases.

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