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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.

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INTRODUCTION

Lipids are large organic molecules that significantly contribute to the progression of cardiovascular diseases. Lipids also have a significant role in forming various biological structures, such as forming the lipid barrier and cell membrane of neurons (1). Lipids are essential for brain structure formation and neuron physiology. The lipid composition governs various brain functions such as perception, mood, and emotional behavior. The eight different categories of lipids involved in the formation of the Central Nervous System (CNS) (2) include Fatty acyls, glycerophospholipids, glycerolipids, sphingolipids, prenol lipids, sterol lipids, polyketides, and saccharolipids.

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. These precursors may include arachidonic acid (ArAc), ceramide, docosahexaenoic acid(DHA), 1,2-diacylglycerol (DAG), lysophosphatidic acid, and phosphatidic acid. The brain's normal physiological function is attributable to these compounds' overall normal function.

Any pathological deviations or injuries to the brain's neuronal structure make decisions for developing neurodegenerative disorders, mental diseases, CNS traumas, and stroke. Once any CNS-damaging diseases or injuries occur, there is no cure for the CNS system, thus contributing to poor quality of life. Several neurological diseases demonstrate the pivotal role of lipids in the signaling and physiology of cells and tissues. A nonregulation in the metabolism of lipids underlies the development and progression of neurodegenerative disorders and neurological diseases. An alteration or change in the normal metabolism of lipids plays a significant role in developing CNS injuries (3).

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. Almost four fifty million individuals globally cannot enjoy this state of mental health. It has been calculated that 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.

Establishing and recognizing the attributing risk factors and efficient treatment plans is a global priority. 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 (4, 5). More importantly, a subnormal level of polyunsaturated omega-3 fatty acids has become a risk factor for mental disorders and can be modified. Long-chain omega-3 Polyunsaturated fatty acid (PUFA) was discovered in the 1970s to be an essential component of brain tissues (6) have been predicted to play crucial roles in the function and development of the brain.

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 (7).

The ever-rising and prevailing level of brain diseases is of great concern. It has been regarded as challenging to global health (8) and has also contributed to increasing the global disease burden. Cognition and neurological performance have been primarily affected by brain disorders and, therefore, can affect an individual's personal and social life.

Research Question

What is the link between lipids and mental health disorders?

Research Justification

The justification for exploring the potential link between lipids and mental health disorders through a comprehensive lipidomic profile analysis is based on several compelling factors:

1. **Emerging biomarker interest:** As the understanding of the molecular underpinnings of mental health disorders advances, there is growing interest in identifying reliable and clinically relevant biomarkers. Lipids are critical in neural function and communication as crucial components of cell membranes and signaling

molecules. Exploring their potential as biomarkers could provide valuable insights into the pathophysiology of mental health disorders.

2. **A holistic approach to mental health:** Mental health disorders are complex and multifaceted, often involving intricate interactions between genetic, environmental, and biochemical factors. Traditional research has primarily focused on neurotransmitters and genetics, but a holistic approach that includes lipidomic profiling can offer a more comprehensive understanding of the underlying mechanisms.
3. **Lipids' role in brain function:** Lipids are integral to brain structure and function, influencing synaptic plasticity, neurotransmission, and neuroinflammation. An in-depth lipidomic analysis could uncover specific lipid species or ratios associated with mental health disorders, shedding light on potential therapeutic targets.
4. **Diagnostic and prognostic potential:** Identifying lipidomic signatures associated with various mental health disorders could lead to the development of diagnostic and prognostic tools. These tools could enhance early detection, personalized treatment strategies, and monitoring of treatment response, ultimately improving patient outcomes.
5. **Drug development and treatment strategies:** Lipid metabolism is a modifiable process, making it a promising target for drug development. Understanding how lipidomic changes are linked to mental health disorders could pave the way for novel therapeutic interventions, including lipid-based treatments or lifestyle modifications.
6. **Translational implications:** Lipidomic profiling has the potential for primary and translational research. Basic research can elucidate the biochemical underpinnings of mental health disorders, while translational research can facilitate the development of practical applications in clinical settings.
7. **Potential for precision psychiatry:** Precision psychiatry aims to tailor treatments to individual patients based on their unique molecular profiles. Lipidomic profiling could contribute to developing a precision medicine approach, allowing clinicians to select the most effective interventions for each patient.
8. **Contribution to the field:** Given the limited understanding of the lipidomic basis of mental health disorders, research in this area can significantly contribute to the field's knowledge base. It could lead to paradigm shifts in our understanding of mental health and open new avenues for research collaboration and interdisciplinary studies.

Investigating the lipidomic profile as a potential link to mental health disorders is a timely and relevant research endeavor that can advance our understanding of these complex conditions, improve diagnosis and treatment strategies, and ultimately enhance the quality of life for individuals affected by mental health disorders.

Lipids and Mental Health Disorders: A Probable Relationship

Lipids may act as signaling molecules or neurotransmitters that contribute to developing mental health disorders. 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. 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.

Alzheimer's disease (A.D.)

A.D. is a progressive brain disorder and a prevalent type of dementia that affects regions of the brain that control cognition and memory. Hence, AD is a human disorder that damages a person's potential to learn, memorize, communicate, reason, and carry out routine tasks. A.D. is classified into two types: an early onset A.D. and a late onset A.D. 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 play a pivotal role in the development of the disease. 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 (1,2, 9). 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. 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. Ab42 has been shown to accelerate the neurodegeneration process as it enhances ceramide production by activating the (N-SMase) neutral sphingomyelinase. 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. (10-12)

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 (13). 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. Reactive oxygen species (ROS) cause the cross-linking of the amyloid-b peptides, thus progressing the degenerative mechanism of A.D. (14).

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. S.N. has been shown that Monoamine oxidase-B is hyperactivated, causing the fall in the level of dopamine in the brain. The process leads to lipid peroxidation and accumulation of ROS.

The activation of the phospholipases in substantia nigra is considered to be a responsible factor. The formation of small agglomerates of an a-synuclein protein called Lewy bodies has been associated with the development of P.D. Apart from the lewy bodies associated with PUFA, all the others remain in a soluble state in the brain. This insolubility of the PUFA-associated Lewy bodies makes them asymptomatic (15-17).

Stimulation of the oligomerization of a-synuclein by docosahexaenoic acid has been reported in studies. 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. Hence DHA can enhance the quality of life of a P.D. patient (18).

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. It is an essential biomarker for evaluating deoxyribonucleic acid (DNA) damage. Several other biomarkers of lipid peroxidation are raised in P.D. patients. Moreover, 4-hydroxy-2- nonrenal has also been found to be raised in P.D. patients and is a product of arachidonic acid peroxidation. The process indicates that P.D. is progressed by lipid peroxidation and accelerating dopamine metabolism (19, 20).

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. Compared to dopamine drugs, blocking the glutamate receptors causes an average person to develop symptoms of schizophrenia. Schizophrenia is characterized by disturbed emotional reactions, thinking, social behavior, hallucinations, and delusions.

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. The two pivotal fatty acids in monoaminergic neurotransmission, synaptic function, and brain development include eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA). Fatty acids are already established to oxidize monoamines responsible for the progression of neurological disorders. EPA and DHA contribute to inhibiting disease progression by increasing the neurotransmission mediated by monoamines.

Huntington's disease (H.D.)

Cognitive decline, behavioral abnormalities, and involuntary movement characterize a neurological disorder, Huntington's disease (H.D.). Research conducted on humans and animals revealed that disrupted cholesterol metabolism is an essential factor in the pathogenesis of H.D. Abnormality in lipid metabolism is associated with the specific action of mutants.

Huntington gene to sterol regulatory binding proteins generally cause a decline in cholesterol levels in affected brain areas. 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. Medications that combat the abnormal lipid milieu are proven beneficial for treat*ing H.D.* (21).

Multiple sclerosis (M.S.)

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 inability to write, speak, and walk. This disease is marked by the high level of ethane and pentane in urine. Both ethane and pentane lead to monounsaturated fatty acid degradation.

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. MDD individuals generally experience sadness or loss of interest in activities of daily living. The individuals cannot perform their daily routine functions appropriately. Cholesterol, with its disrupted metabolism, causes major depressive disorder. Cholesterol plays a vital role in regulating ion channels and membrane-bound proteins.

Furthermore, it is required to form dendrites, synapses, and axons. It decreases synaptic plasticity and failed neurotransmission when impaired, leading

to MDD. Cholesterol-rich diet is promising in treating MDD (23).

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.

The eight categories of lipids obtained from prokaryotic or eukaryotic sources are biomarkers for neurodegenerative disorders are Fatty acids and hydroxyl fatty acids, Glycerolipids, Glycerophospholipids, Sphingolipids, Sterol lipids, Sacchrolipids, Prenol lipids, and polyketides. These carry out a variety of biological functions that act as biomarkers for understanding mental 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.

Research Limitations

While exploring the potential link between lipids and mental health disorders through lipidomic profiling holds promise, there are several limitations and challenges that researchers should consider:

1. **Sample heterogeneity:** Mental health disorders encompass various conditions with diverse etiologies and symptom presentations. Obtaining a homogeneous and representative sample that accurately reflects the complexity of these disorders can be challenging, potentially leading to variability in lipidomic profiles.
2. **Causality and correlation:** Establishing a causal relationship between specific lipidomic changes and mental health disorders is complex. Lipid alterations could result from the disorder rather than a causal factor, making it difficult to determine whether observed changes are a cause or an effect.
3. **Biological variability:** Lipidomic profiles can vary significantly between individuals due to genetics, diet, lifestyle, and environmental exposures. Distinguishing between variations associated with mental health disorders and those due to other factors requires careful control and statistical analysis.
4. **Technology and methodological challenges:** Lipidomic profiling techniques continually evolve, and different methods may yield varying results. Standardizing protocols and accounting for potential technical biases is essential to ensure the reliability and comparability of findings across studies.
5. **Ethical considerations:** Research involving human participants, especially those with mental health disorders, raises ethical considerations regarding informed consent, privacy, and potential stigmatization. Ensuring participant well-being and obtaining informed consent can be particularly complex in vulnerable populations.
6. **Longitudinal studies and dynamic changes:** Mental health disorders often involve dynamic symptoms and disease progression changes. Cross-sectional lipidomic analyses may not capture temporal changes accurately, necessitating longitudinal studies that can be resource-intensive and require careful participant retention.
7. **Comorbidity and confounding factors:** Many individuals with mental health disorders also experience physical health conditions and lifestyle factors that can influence lipid metabolism. Untangling the specific contributions of these factors to lipidomic changes presents a challenge.
8. **Data analysis and interpretation:** The analysis of large-scale lipidomic datasets requires sophisticated bioinformatics tools and expertise.

Ensuring robust statistical methods and appropriate data interpretation is crucial to avoid spurious associations.

9. **Generalizability:** Findings from lipidomic studies may not be directly applicable to all mental health disorders or populations. Results may have limited generalizability to different age groups, ethnicities, and cultural contexts.
10. **Translation to clinical practice:** While promising, translating lipidomic findings into clinically actionable insights or therapeutic interventions requires rigorous validation and extensive clinical trials, which can be time-consuming and costly.
11. **Availability of reference databases:** Comprehensive lipidomic analysis relies on reference databases for lipid identification and quantification. The availability and quality of these databases can impact the accuracy and reproducibility of results.

Addressing these limitations requires careful study design, collaboration across disciplines, and ongoing advancements in lipidomic profiling techniques. While these challenges may pose obstacles, they also underscore the need for a thoughtful and comprehensive approach to investigating the potential link between lipids and mental health disorders.

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. Further understanding using in vitro, in vivo, and silico studies must be conducted to diagnose and treat mental disorders by controlling pathogenic lipids.

RECOMMENDATIONS

Here are some recommendations for researchers looking to explore the potential link between lipids and mental health disorders through lipidomic profiling:

1. **Collaborative interdisciplinary research:** Given the complexity of mental health disorders and lipid biology, collaborate with experts from diverse fields such as psychiatry, neuroscience, lipidomics, bioinformatics, and statistics. Interdisciplinary collaboration can enrich study design, data analysis, and interpretation.
2. **Careful study design:** Design studies that carefully consider sample size, participant demographics, inclusion/exclusion criteria, and control groups. Longitudinal studies and well-matched control groups can address some limitations related to sample heterogeneity and causal inference.
3. **Ethical considerations:** Prioritize ethical considerations by obtaining informed consent, ensuring participant confidentiality, and addressing potential stigmatization. Collaborate with ethics committees and mental health professionals to navigate sensitive issues.
4. **Standardization of protocols:** Utilize established protocols for lipid extraction, quantification, and identification to ensure consistency and comparability of results across studies. Validate the chosen methods and techniques using appropriate standards and controls.
5. **Advanced lipidomic techniques:** Stay updated with the latest developments in

lipidomic profiling technologies. Consider using advanced techniques such as mass spectrometry and liquid chromatography to achieve higher resolution and accuracy in lipid identification and quantification.

6. **Longitudinal studies:** Incorporate longitudinal study designs to capture dynamic changes in lipidomic profiles over time. Longitudinal data can provide insights into the progression of mental health disorders and the potential role of lipidomic changes.
7. **Statistical rigor:** Employ robust statistical methods to analyze lipidomic data. Correct for multiple testing, control for confounding variables, and consider employing machine learning approaches to identify meaningful patterns within complex datasets.
8. **Validation and replication:** Validate findings in independent cohorts and, if possible, across different populations. Replication of results enhances the reliability and generalizability of findings.
9. **Clinical relevance:** Connect lipidomic findings to clinical outcomes by investigating correlations with symptom severity, treatment response, and functional outcomes. It can bridge the gap between basic research and clinical practice.
10. **Biomarker development:** Evaluate the diagnostic and prognostic potential of identified lipidomic markers. Develop prediction models that combine lipidomic data with other relevant clinical, genetic, and environmental factors.
11. **Mechanistic studies:** Complement lipidomic profiling with mechanistic studies to elucidate the biological pathways through which lipidomic changes might contribute to mental health disorders. Animal models, cell culture systems, and in vitro experiments can provide mechanistic insights.
12. **Translation to therapeutics:** While considering the potential for lipid-based interventions, collaborate with pharmaceutical researchers to explore the development of lipid-targeted therapies. Preclinical and clinical trials are necessary to establish the safety and efficacy of such interventions.
13. **Open science practices:** Embrace open science practices by sharing data, methodologies, and results with the scientific community. It fosters transparency, facilitates collaboration, and accelerates progress in the field.
14. **Educational initiatives:** Engage in public outreach and education to raise awareness about the potential link between lipids and mental health. Communicate findings to clinicians, policymakers, and the general public to promote informed decision-making.
15. **Adaptability and flexibility:** Recognize that the lipidomics and mental health field is evolving. Remain adaptable to new insights, technological advancements, and emerging research questions.
16. Incorporating these recommendations into your research approach can enhance your investigation's rigor, relevance, and impact on the potential connection between lipids and mental health disorders.

Research Implications

Exploring the potential link between lipids and mental health disorders through lipidomic profiling has several essential research implications that can contribute to the advancement of science, clinical practice, and public health:

1. **Enhanced understanding of mental health disorders:** Investigating the lipidomic profile's role in mental health disorders can provide deeper insights

into the underlying biochemical mechanisms. This understanding can help refine existing theories, develop new hypotheses, and expand our comprehension of the complex nature of these disorders.

2. **Biomarker discovery and diagnostic tools:** Identifying specific lipidomic markers associated with different mental health disorders could lead to the developing of objective and reliable diagnostic tools. These biomarkers could aid clinicians in earlier and more accurate diagnoses, enabling timely interventions.
3. **Personalized treatment strategies:** A better understanding of the lipidomic basis of mental health disorders can facilitate the development of personalized treatment strategies. Tailoring interventions based on an individual's lipidomic profile could enhance treatment efficacy and reduce the trial-and-error approach in medication selection.
4. **Novel therapeutic targets:** Uncovering lipidomic alterations linked to mental health disorders can reveal novel therapeutic targets. It could lead to the development of innovative drugs and interventions that modulate lipid metabolism, potentially offering new avenues for treatment.
5. **Predictive and prognostic insights:** Lipidomic profiles could provide predictive and prognostic insights into disease progression and treatment response. Clinicians could use these insights to adjust treatment plans and optimize patient care.
6. **Integration with precision medicine:** Incorporating lipidomic data into the growing field of precision medicine can enhance the ability to deliver targeted and individualized treatments for mental health disorders. This integration could lead to more effective and efficient therapeutic interventions.
7. **Validation of lifestyle interventions:** Understanding how lipid metabolism is influenced by lifestyle factors such as diet, exercise, and stress could validate the importance of holistic approaches to mental health management. Lifestyle interventions may complement pharmacological treatments.
8. **Biological mechanisms for drug development:** Lipidomic research may uncover specific lipid pathways that drug therapies can target. It could expedite drug development efforts and lead to innovative medications with fewer side effects.
9. **Early intervention and prevention:** Lipidomic profiling might contribute to the identification of individuals at higher risk of developing mental health disorders. Early intervention and preventive strategies could be designed to mitigate risk factors and promote mental well-being.
10. **Holistic treatment approaches:** Integrating lipidomic information with other omics data (genomic, proteomic, metabolomic) could lead to a more comprehensive understanding of mental health disorders. This holistic approach could inform multifaceted treatment approaches.
11. **Research collaboration and funding opportunities:** Exploiting lipids' role in mental health could foster interdisciplinary collaborations between lipidomics researchers, psychiatrists, neuroscientists, and other experts. It could also attract funding for innovative research projects.
12. **Educational outreach and public awareness:** Lipidomic research findings can contribute to public awareness campaigns and educational initiatives about the biological basis of mental

health disorders. This understanding may help reduce stigma and promote informed discussions about mental health.

13. **Data integration and big data analytics:** Integrating large-scale lipidomic datasets with other biomedical data can contribute to developing comprehensive models that capture the complexity of mental health disorders. Advanced analytics can identify patterns and correlations that may not be apparent through individual datasets.

Overall, research into the lipidomic profile's potential link to mental health disorders holds the promise of transforming our understanding, diagnosis, and treatment of these conditions, ultimately leading to improved mental health outcomes for individuals and society.

Future Research Directions

Future research exploring the potential link between lipids and mental health disorders through lipidomic profiling should address current gaps, refine methodologies, and delve deeper into the underlying mechanisms. Here are some promising future research directions:

1. **Longitudinal studies:** Conducting longitudinal studies that follow individuals over extended periods can reveal dynamic changes in lipidomic profiles associated with the onset, progression, and remission of mental health disorders. This approach can help establish temporal relationships and distinguish between causal and consequential lipidomic changes.
2. **Causal inference:** Employ innovative study designs like Mendelian randomization to explore causal relationships between lipidomic changes and mental health disorders. These designs can help determine whether lipidomic alterations play a direct role in developing or exacerbating these disorders.
3. **Multi-omics integration:** Integrate lipidomic data with other omics data (genomic, proteomic, metabolomic) to construct comprehensive molecular profiles of mental health disorders. Multi-omics approaches can provide a more holistic understanding of the complex interactions underlying these conditions.
4. **Functional validation:** Conduct mechanistic studies to validate the functional significance of lipidomic changes identified in association with mental health disorders. Animal models, cell culture systems, and organoids can help elucidate the impact of lipid alterations on neural function and behavior.
5. **Neuroinflammation and the immune system:** Investigate the role of lipids in neuroinflammation and the immune response within the context of mental health disorders. Lipids can influence immune cell function and neuroinflammatory processes, potentially contributing to disease pathogenesis.
6. **Microbiome-Lipid-Brain axis:** Explore the intricate connections between the gut microbiome, lipid metabolism, and brain health. Investigate how microbial metabolites and lipids interact to influence mental health and the development of psychiatric disorders.
7. **Lipid subtype analysis:** Delve into specific lipid subclasses, such as phospholipids, sphingolipids, and fatty acids, to identify subtype-specific changes associated with mental health disorders. Subtype analysis can provide more targeted insights into the lipidomic basis of these conditions.
8. **Sex differences:** Investigate potential sex differences in lipidomic profiles associated with mental health disorders.

Hormonal influences on lipid metabolism and brain function may contribute to sex-specific patterns of lipidomic changes.

9. **Advanced imaging techniques:** Combine lipidomic profiling with advanced neuroimaging techniques, such as magnetic resonance spectroscopy (MRS), to explore the spatial distribution of lipid alterations within the brain regions implicated in mental health disorders.
10. **Machine learning and A.I.:** Utilize machine learning and artificial intelligence algorithms to analyze complex lipidomic datasets and uncover subtle patterns that may indicate specific mental health disorders. These methods can enhance predictive modeling and biomarker discovery.
11. **Therapeutic interventions:** Translate lipidomic findings into targeted therapeutic interventions, including developing lipid-based treatments, dietary interventions, and lifestyle modifications that can modulate lipid metabolism to improve mental health outcomes.
12. **Patient stratification:** Use lipidomic profiling to stratify patients into subgroups based on shared lipidomic characteristics. It can facilitate more precise treatment approaches and enhance the success of clinical trials by identifying subpopulations that are more likely to respond to specific interventions.
13. **Real-world applications:** Explore the feasibility of incorporating lipidomic profiling into clinical practice. Develop user-friendly tools for lipidomic data interpretation, integration into electronic health records, and incorporation into routine mental health assessments.
14. **Global diversity:** Investigate how lipidomic profiles associated with mental health disorders vary across different ethnicities, cultures, and geographic regions. Considering global diversity can provide a more comprehensive understanding of these conditions' universality and context-specific aspects.
15. **Public health impact:** Assess the potential public health impact of lipidomic-based interventions for mental health. Consider the cost-effectiveness, scalability, and accessibility of lipidomic profiling in different healthcare settings.

By pursuing these future research directions, the field can advance our understanding of the lipidomic basis of mental health disorders, unravel novel therapeutic opportunities, and ultimately improve the lives of individuals affected by these conditions.

DECLARATION

All authors contributed equally.

COMPETING INTERESTS

There is no conflict of interest among the authors.

CONSENT FOR PUBLICATION

All authors agreed to the Publication.

REFERENCES

1. Gary R. Investigating the role of lipids in mood, aggression, and schizophrenia. Psychiatric services. 1997 Jul 4;48(7):875.
2. Fahy E, Subramaniam S, Brown HA, Glass CK, Merrill AH, Murphy RC, Raetz CR, Russell DW, Seyama Y, Shaw W, Shimizu T. Acomprehensive classification system for lipids1. Journal of lipid research. 2005 May 1;46(5):839-61.
3. Adibhatla RM, Hatcher JF, Dempsey RJ. Lipids and lipidomics in brain injury and diseases. The AAPS journal. 2006 Jun;8:E314-21.

4. Gómez-Pinilla F. Brain foods: the effects of nutrients on brain function. Nature reviews neuroscience. 2008 Jul;9(7):568-78.
5. Larsen EC, Hatcher JF, Adibhatla RM. Effect of tricyclodecan-9-yl potassium xanthate (D609) on phospholipid metabolism and cell death during oxygen–glucose deprivation in PC12 cells. Neuroscience. 2007 May 25;146(3):946-61.
6. Crawford MA, Sinclair AJ. Nutritional influences in the evolution of mammalian brain. InCiba Foundation Symposium 3-Lipids, Malnutrition & the Developing Brain 1972 Jan 1 (Vol. 3, pp. 267-292). Chichester, UK: John Wiley & Sons, Ltd..
7. Sinn N, Milte C, Howe PR. From ADHD to Alzheimer's: omega-3 fatty acids and mental health. 2009.
8. Wittchen HU, Jacobi F, Rehm J, Gustavsson A, Svensson M, Jönsson B, Olesen J, Allgulander C, Alonso J, Faravelli C, Fratiglioni L. The size and burden of mental disorders and other disorders of the brain in Europe 2010. Europeanneuropsychopharmacolog 2011 Sep 1;21(9):655-79.
9. Jiang J, Borisenko GG, Osipov A, Martin I, Chen R, Shvedova AA, Sorokin A, Tyurina YY, Potapovich A, Tyurin VA, Graham SH. Arachidonic acid-induced carbon-centered radicals and phospholipid peroxidation in cyclo-oxygenase-2-transfected PC12 cells. Journal of neurochemistry. 2004 Sep;90(5):1036-49.
10. Kunz A, Anrather J, Zhou P, Orio M, Iadecola C. Cyclooxygenase-2 does not contribute to postischemic production of reactive oxygen species. Journal of Cerebral Blood Flow & Metabolism. 2007 Mar;27(3):545-51.
11. Delacourte A, Sergeant N, Champain D, Wattez A, Maurage CA, Lebert F, Pasquier F, David JP. Nonoverlapping but synergetic tau and APP pathologies in sporadic Alzheimer's disease. Neurology. 2002 Aug 13;59(3):398-407.
12. Ehehalt R, Keller P, Haass C, Thiele C, Simons K. Amyloidogenic processing of the Alzheimer β-amyloid precursor protein depends on lipid rafts. The Journal of cell biology. 2003 Jan 6;160(1):113-23.
13. Whitfield JF. Can statins put the brakes on Alzheimer's disease?. Expert opinion on investigational drugs. 2006 Dec 1;15(12):1479-85.
14. Oddo S, Billings L, Kesslak JP, Cribbs DH, LaFerla FM. Aβ immunotherapy leads to clearance of early, but not late, hyperphosphorylated tau aggregates via the proteasome. Neuron. 2004 Aug 5;43(3):321-32.
15. Farooqui AA, Ong WY, Horrocks LA. Inhibitors of brain phospholipase A2 activity: their neuropharmacological effects and therapeutic importance for the treatment of neurologic disorders. Pharmacological reviews. 2006 Sep 1;58(3):591-620.
16. Hauser RA, Zesiewicz TA. Advances in the pharmacologic management of early Parkinson disease. The Neurologist. 2007 May 1;13(3):126-32.
17. Welch K, Yuan J. α-Synuclein oligomerization: a role for lipids?. Trends in neurosciences. 2003 Oct 1;26(10):517-9.
18. Sharon R, Bar-Joseph I, Frosch MP, Walsh DM, Hamilton JA, Selkoe DJ. The formation of highly soluble oligomers of α-synuclein is regulated by fatty acids and enhanced in

Parkinson's disease. Neuron. 2003 Feb 20;37(4):583-95.
19. Larsen EC, Hatcher JF, Adibhatla RM. Effect of tricyclodecan-9-yl potassium xanthate (D609) on phospholipid metabolism and cell death during oxygen–glucose deprivation in PC12 cells. Neuroscience. 2007 May 25;146(3):946-61.
20. Maxfield FR, Tabas I. Role of cholesterol and lipid organization in disease. Nature. 2005 Dec 1;438(7068):612-21.
21. Muma NA. Transglutaminase is linked to neurodegenerative diseases. Journal of Neuropathology & Experimental Neurology. 2007 Apr 1;66(4):258-63.
22. Müller CP, Reichel M, Mühle C, Rhein C, Gulbins E, Kornhuber J. Brain membrane lipids in major depression and anxiety disorders. Biochimica et Biophysica Acta (BBA)-Molecular and Cell Biology of Lipids. 2015 Aug 1;1851(8):1052-65.