Beyond comorbidities: metabolic dysfunction as a root cause of neuropsychiatric disorders†

COMMENTARY

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SUMMARY

Metabolic dysfunction has been long associated with severe mental illness (SMI), often viewed as a comorbidity to be managed. However, emerging evidence suggests that metabolic dysfunction, particularly at the mitochondrial level, may be a foundational element in the pathophysiology of neuropsychiatric disorders. This commentary expands on the current understanding by exploring the brain energy theory of mental illness, which posits that mitochondrial dysfunction is central to both metabolic and psychiatric conditions. The roles of insulin resistance, chronic stress and environmental factors are highlighted as shared biopsychosocial determinants that contribute to deterioration in both metabolic and mental health. The therapeutic potential of the ketogenic diet is discussed, particularly its ability to improve mitochondrial function and alleviate psychiatric symptoms. This shift in perspective, from viewing metabolic dysfunction as a secondary concern to recognising it as a root cause of SMI, has significant implications for clinical practice and research. By focusing on bioenergetic deficits and mitochondrial health, psychiatry may advance towards more effective, integrated treatment approaches that target the underlying cellular dysfunctions driving both metabolic and mental illnesses.

KEYWORDS

Mitochondria; ketogenic; metabolism; psychotic disorders/schizophrenia; bipolar type I or II disorders.

Needham et al offer us a timely and comprehensive overview of the complex interplay between severe mental illness (SMI) and metabolic dysfunction (Needham 2025, this issue). They astutely recognise the bidirectional relationship between these two domains, acknowledging that metabolic dysfunction can precede the onset of SMI. This recognition is a crucial step forwards, yet there remains an opportunity to expand on this understanding by considering the shared biopsychosocial root causes of both metabolic and neuropsychiatric disorders. This perspective deepens our comprehension of the connection between metabolism and mental illness, offering novel avenues for treatment and research that could reshape the field of psychiatry.

Expanding beyond bidirectionality: the brain energy theory

Needham et al accurately describe the bidirectional relationship between metabolic dysfunction and SMI, highlighting how metabolic issues can precede, accompany or follow the onset of mental illness (Needham 2024, this issue). However, they are still seen primarily as comorbidities that need to be managed. In what I have called the brain energy theory of mental illness, I go further and propose that metabolic dysfunction – particularly at the mitochondrial level – is not just an associated feature but a foundational element in the pathophysiology of SMI (Palmer 2022). Certain psychiatric medications, particularly antipsychotics, are known to exacerbate metabolic syndrome, compounding the metabolic challenges often seen in individuals with SMI (Orsolini 2020). This connection highlights the need for treatment models that prioritise metabolic health in the management of SMI.

One point to emphasise is that insulin resistance, often seen in individuals with SMI, is not a root cause unto itself but rather a sign of deeper metabolic and mitochondrial dysfunction (Kim 2008). The same biopsychosocial factors – often referred to as 'social determinants of health' – that contribute to mental illness also play a significant role in insulin resistance and metabolic dysfunction. These include factors such as chronic stress, trauma, poor diet, lack of physical activity and socioeconomic conditions, which simultaneously drive deterioration in both mental and metabolic health. This overlap suggests that psychiatric and metabolic conditions share more than coincidental comorbidity: they may emerge from the same underlying cellular dysfunctions.

Mitochondria and mental health: an overlooked connection

Mitochondria, the cellular powerhouses, are central to the brain energy theory. They generate the energy

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necessary for maintaining neuronal function, but research over the past two decades has revealed numerous additional mitochondrial roles that have long been implicated in mental disorders. These functions include calcium homeostasis, epigenetic regulation, oxidative stress response, inflammation control, and the synthesis and regulation of neurotransmitters and hormones – all processes known to be disrupted in conditions such as bipolar disorder, schizophrenia and major depressive disorder (Monzel 2023; Ni 2024).

By placing mitochondrial dysfunction at the core of psychiatric pathophysiology, the brain energy theory provides a unifying framework to explain how disruptions in cellular energy metabolism, oxidative stress and neuroinflammation can converge to create the conditions for mental illness. Mitochondrial dysfunction could manifest as symptoms that we traditionally categorise under distinct psychiatric labels, yet the root issue may be a common bioenergetic failure at the cellular level.

Mitochondrial dysfunction: a core component of SMI

Although Needham et al's article touches on genetic and biological factors contributing to metabolic dysfunction, it could benefit from a more detailed exploration of mitochondrial dysfunction as a central mechanism in SMI. Recent research has identified various biomarkers of mitochondrial dysfunction in people with SMI, such as altered mitochondrial DNA copy numbers, reduced adenosine triphosphate (ATP) production and increased oxidative stress markers (Ng 2008). These findings suggest that addressing mitochondrial health could be a key therapeutic target, not only for improving metabolic outcomes but also for directly alleviating psychiatric symptoms.

For example, in bipolar disorder, studies have shown that mitochondrial dysfunction correlates with disease state and severity (Scaini 2021). In schizophrenia, altered mitochondrial function has been linked to cognitive deficits and negative symptoms (Fizíková 2023). These associations underscore the need to consider mitochondrial health as a fundamental aspect of psychiatric care, shifting the focus from merely treating symptoms to addressing the underlying cellular dysfunction.

The ketogenic diet: a metabolic and mitochondrial intervention

Needham et al rightly highlight the potential of a ketogenic diet as a therapeutic intervention for metabolic dysfunction in SMI, particularly because of its effects on weight, glucose levels and overall metabolic health. However, the ketogenic diet offers even more profound potential benefits, extending beyond its metabolic effects to directly affecting brain function through mitochondrial mechanisms.

Ketone bodies such as beta-hydroxybutyrate, produced during a ketogenic diet, are not only an alternative energy source for the brain but also possess neuroprotective properties. They can enhance mitochondrial function, reduce oxidative stress and modulate neurotransmitter systems – all of which are crucial in managing the bioenergetic deficits seen in SMI (Rho 2017). The potential of the ketogenic diet to improve both psychiatric symptoms and metabolic health through these mechanisms positions it as a powerful, albeit underutilised, tool in psychiatry.

Although randomised controlled trials are still needed to establish the efficacy of the ketogenic diet in SMI, preliminary evidence and case reports are promising. Integrating such metabolic therapies into psychiatric treatment plans, especially for individuals with treatment-resistant SMI, holds promise.

Embracing a new paradigm in psychiatry: from management to transformation

Needham et al's original article offers valuable insights into managing metabolic dysfunction in SMI, emphasising the need for routine monitoring and lifestyle interventions. However, the brain energy theory advocates for a broader, more transformative approach. Rather than viewing metabolic dysfunction as a comorbidity to be managed, this model suggests that improving metabolic health – particularly mitochondrial function – should be central to psychiatric treatment.

This approach requires a paradigm shift in how we think about mental illness. Metabolic and mitochondrial health should not be afterthoughts in psychiatric care but should be integral to the diagnosis, treatment and prevention of mental illness. This shift has significant implications for clinical practice, where metabolic therapies could be prioritised alongside psychopharmacological and psychotherapeutic interventions.

Clinicians should be trained to recognise the signs of metabolic and mitochondrial dysfunction and incorporate metabolic health assessments into routine psychiatric evaluations. By adopting a comprehensive approach that considers the brain's energy needs as a central component of mental health, we can develop more effective, personalised treatment plans that address both the metabolic and psychiatric aspects of illness.

Recommendations for integrative care

Translating the brain energy theory into clinical practice involves adopting an integrative approach

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that includes metabolic health as a core component of psychiatric treatment. Clinicians should monitor patients with SMI for signs of mitochondrial and metabolic dysfunction, particularly when prescribing medications that may contribute to metabolic syndrome. Regular metabolic health assessments, including monitoring biomarkers of insulin resistance, lipid profiles and inflammation, as well as interventions such as dietary counselling (e.g. exploring ketogenic diets for those suitable), exercise programmes and lifestyle modifications may be essential adjuncts to pharmacological and psychotherapeutic treatments. This holistic approach could improve both metabolic and psychiatric outcomes, potentially transforming patient care in real-world settings.

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