

The Emerging Field of Nutritional Mental Health: Inflammation, the Microbiome, Oxidative Stress, and Mitochondrial Function

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Abstract

We live in a transformational moment for understanding the etiology of mental disorders. The previous leap in understanding occurred 60 years ago, which led us to incorporate psychopharmacology into our curricula to address the chemical basis of neurotransmitter function, especially as explained through the then-popular catecholamine hypothesis. The current revolution is broader, consisting of the rapidly accumulating knowledge of how inflammation, microbiome imbalance (gut dysbiosis), oxidative stress, and impaired mitochondrial output affect brain function. Suitable interventions for fighting inflammation, restoring normal gut function, reducing oxidative stress, and improving mitochondrial metabolism incorporate lifestyle variables, including nutrients and probiotics. This article invites readers to stay abreast of this emerging model of the biological basis of mental illness, given that it has particular relevance for those readers interested in alleviating the suffering of individuals with mental disorders. This overview describes the basis for a new field in mental health: nutritional psychiatry/psychology.

Keywords

mental health, nutritional sciences, oxidative stress, microbiome, mitochondria

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In the mid-1960s, psychiatry researchers developed what became known as the catecholamine or biogenic amine hypothesis of mood disorders, which led to the concept that abnormal mood states were caused by imbalances in neurotransmitters such as serotonin. Although the public still embraces the construct of “chemical imbalance” as a full explanation of etiology, the theory seems impossibly superficial and vague by 21st-century standards. As Gardner and Boles (2005) pointed out in their seminal article “Beyond the Serotonin Hypothesis,” there is still a role for neurotransmitters such as serotonin in the new models, but only when embedded in a current understanding of brain metabolism. Metabolic mechanisms currently being studied extensively relate to inflammation, the microbiome, oxidative stress, and impaired mitochondrial function. It is particularly imperative that

mental-health professionals understand the treatment implications of these new discoveries and models, given that the most appropriate therapeutic approaches often involve lifestyle modifications that are within their scope of practice (Walsh, 2011). The overview presented here summarizes the literature that constitutes the basis for a new field in mental health: nutritional psychiatry/psychology.

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Inflammation and Mental Health

It has been almost 25 years since Maes et al. (1990) first reported enhanced immune activity in major depression. In the ensuing decades, the “immunity hypothesis” of depression has been strongly supported: Depression is associated with activation of inflammatory responses (Berk et al., 2013; Dowlati et al., 2010). Studies on mental health in relation to low-grade, systemic inflammatory activity often employ serum levels of biomarkers, such as the amino acid homocysteine (associated with elevated risk of cardiovascular disease), C-reactive protein (which rises in response to inflammation or infection), or any of a series of cytokines (cell-signaling molecules involved in intracellular communication) that promote systemic inflammation, especially tumor necrosis factor alpha (TNF-alpha) and Interleukin 6 (IL-6). One example of this type of research is the Cooper Center Study of almost 12,000 adults: Elevated homocysteine levels were associated with 26% increased odds of scoring in the depression range on the Center for Epidemiologic Studies Depression Scale, even after researchers controlled for many variables likely to influence both inflammation and depression (e.g., age, sex, body mass index, exercise; Gu et al., 2012; Reber, 2012). A meta-analytic review of the role of cytokines in depression reported that in spite of some inconsistent findings, the association of TNF-alpha and IL-6 with diagnosed depression was strongly supported (Dowlati et al., 2010).

Abundant evidence from both experimental and clinical studies has shown that inflammation can induce symptoms of depression (Dantzer, 2012), which has led to a lively debate about whether inflammation causes depression, depression causes inflammation, or both. Even longitudinal data suggest that the causal relationships are complex, with depression sometimes preceding elevations in biomarkers of inflammation, and the biomarker elevation sometimes preceding symptoms of depression.

Inflammatory processes have also been demonstrated in bipolar disorder (Hamdani, Tamouza, & Leboyer, 2012) and psychosis (Borovcanin et al., 2012), although, again, the picture is complicated. In a few cases, some inflammatory biomarkers have shown the elevated levels expected in association with symptom severity, but other inflammatory markers have been low, thereby resulting in the hypothesis that lower markers of inflammation may indicate the body’s attempt to limit proinflammatory processes. Given the overall strength of the data associating inflammation with mental-health symptoms, it is relevant that a meta-analysis of clinical trials of nonsteroidal anti-inflammatory drugs (NSAIDs) used as adjuncts in treatment for schizophrenia showed a mean effect size of 0.43, indicating that the NSAIDs (celecoxib in four studies, and aspirin in the fifth) had a moderately beneficial impact on

symptoms (Sommer, de Witte, Begemann, & Kahn, 2012). In terms of etiology, the logical question is this: What causes systemic, chronic inflammation? One very promising area of research focuses on the role of the gastrointestinal (GI) system.

The Microbiome and Mental Health

It is amazing to contemplate the implications of the fact that at least 90% of the cells in and on our bodies are not human: They are the microbial cells (especially bacteria) that constitute our microbiome. Most reside in the GI system, where they protect the intestinal barrier defense system, digest our food, extract the nutrients that we need, and in some cases synthesize those nutrients for us (Carpenter, 2012). This ecological community of 10^{13} to 10^{14} microorganisms in the GI tract is an integral part of the system of bidirectional communication between the gut and the brain, termed the “gut-brain axis.” An imbalance in gut bacteria (dysbiosis) can have various negative repercussions for the host, including the potential for overgrowth of already-present opportunistic microorganisms, such as *Clostridium difficile*, a decrease in production of short-chain fatty acids, and an increased susceptibility to intestinal pathogens (Bailey et al., 2011). Evidence has suggested that the depletion or absence of beneficial bacteria that promote the development of the immune system can lead to the induction of inflammatory responses (Berk et al., 2013) and that this altered immune response could underlie many known chronic inflammatory disorders, including inflammatory bowel disease, rheumatoid arthritis (Round & Mazmanian, 2009), and possibly—as mentioned earlier—some mental disorders, particularly depression, which has been strongly associated with increased inflammatory activation (Berk et al., 2013).

There are many possible causes of gut dysbiosis, including the use of broad-spectrum antibiotics, a poor diet, and the modern environment’s being too clean (the hygiene, or “Old Friends,” hypothesis; Hawrelak & Myers, 2004; Rook, Raison, & Lowry, 2012). Psychological stress also appears to have a significant effect on the composition of the microbiota: This has been shown in animal models prenatally (Bailey, Lubach, & Coe, 2004), in early life (Bailey & Coe, 1999; Berk et al., 2013), and in adulthood (Bailey et al., 2011). These effects can last for a long time: Changes to the gut microbiota of rats that had undergone maternal separation 3 hr per day for 10 days after birth were maintained through to adulthood (O’Mahony et al., 2009). In observing these long-term effects, together with changes in behavior, systemic immune responses, and hypothalamic-pituitary-adrenal (HPA) axis function, O’Mahony et al. (2009) concluded that early life stress induces persistent changes to the

gut-brain axis and that these changes could contribute to symptoms of irritable bowel syndrome and psychiatric disorders in adulthood. This effect of psychological stress on the microbiota has also been demonstrated in humans (Knowles, Nelson, & Palombo, 2008).

Several studies have suggested that administering probiotic bacteria can affect emotional behavior in animal models (Bravo et al., 2011; Desbonnet et al., 2010; Desbonnet, Garrett, Clarke, Bienenstock, & Dinan, 2008; Messaoudi et al., 2010). For example, Bravo et al. (2011) treated healthy mice with a probiotic formulation containing *Lactobacillus rhamnosus* or a placebo and then subjected all animals to a battery of anxiety- and depression-related behavioral tests. Results showed that chronic treatment with *Lactobacillus rhamnosus* reduced anxiety- and depression-related behavior. This study also showed that probiotic administration induced region-dependent alterations in GABA in the brains of the mice. GABA is the main inhibitory neurotransmitter in the mammalian central nervous system, and alterations in its receptor expression are implicated in the development of anxiety and depression (Cryan & Kaupmann, 2005). In addition, the neurochemical and behavioral effects were not seen in mice whose vagus nerve was surgically severed, identifying the vagus nerve as a plausible major communication pathway between the gut microbiota and the brain.

A recent study by Tillisch et al. (2013) provided the first direct demonstration that ingestion of probiotic bacteria can modulate brain activity in humans. Healthy women drank a fermented milk product with probiotic bacteria, a nonfermented milk product, or nothing; functional MRI revealed robust alterations in the brain activity of those participants who consumed the probiotic bacteria relative to the comparison groups. This effect of probiotic bacteria on brain function confirms the link between the gut microbiota and the brain and leads to the possibility of using probiotics alone as interventions for psychological symptoms, as has been suggested both recently (e.g., Logan & Katzman, 2005) and historically in the time of “auto-intoxication” theories of mental disorders (e.g., Phillips, 1910). Although effects of probiotics on mood and anxiety have been shown in some recent trials (e.g., Messaoudi et al., 2010; Rao et al., 2009), so far, the evidence for using probiotics alone for the treatment of psychological symptoms is insubstantial. Additional randomized, placebo-controlled trials in clinical populations with positive outcomes are needed before any real claims of efficacy can be made.

As mentioned earlier, one system implicated in the gut-brain axis is the HPA axis. Sudo et al. (2004), in the first study to show that normal microbes affect the neural network responsible for stress responsiveness, found significantly exaggerated HPA responses to stress in germ-free

animals (animals with no microorganisms living in or on them). It is interesting that the exaggerated HPA responsiveness could be reversed by repopulation of the gut with *Bifidobacterium infantis*. Maes et al. (1993) had previously proposed that the HPA hyperactivity seen in depression can be induced by proinflammatory cytokines, which suggests that the underlying mechanism may be the induction of inflammatory responses in conditions of dysbiosis.

One plausible way that dysbiosis in the gut microbiome could lead to increased inflammatory activation is through an increase in immune responses against elements produced by some potentially toxic gram-negative bacteria normally present in the intestines, such as the endotoxin lipopolysaccharide (LPS; part of the bacterial wall of gram-negative bacteria; Berk et al., 2013). Increased plasma levels of immunoglobulin A or M (IgA/IgM; blood-based antibodies) have recently been demonstrated in clinical depression (e.g., Maes, Kubera, Leunis, & Berk, 2012). Berk et al. (2013) proposed that the presence of increased plasma immunoglobulins is indicative of an immune response against LPS, thereby suggesting a pathway by which dysbiosis can lead to increased inflammatory responses. It is interesting that electrical stimulation of the vagus nerve—mentioned earlier as having an important role in the gut-brain axis—has been shown to limit this systemic inflammatory response to LPS in rats (Borovikova et al., 2000).

One other mechanism suggested by Maes et al. (2013), which may explain the increased immune response in depression, is bacterial translocation—the migration of bacteria to areas outside the intestinal tract—which can happen in states of dysbiosis when the integrity of the mucosal barrier is compromised. Mucosal cells in the gut normally form a barrier that is virtually impermeable to fluid by forming tight junctions where two cell membranes join together by forming a network of protein strands. This tight junction barrier normally segregates gram-negative bacteria from the host’s immune cells. In cases where the mucosal barrier is compromised by the loosening of the tight junctions, gram-negative bacteria may translocate from the gut into various areas outside of the intestine, including, for example, the mesenteric lymph nodes (Berg & Garlington, 1979). Given that, under normal conditions, immune cells are separated from gram-negative bacteria, they are not primed against the LPS contained within the gram-negative bacteria and so will become activated on contact with gram-negative bacteria. This activation leads to the induction of inflammatory pathways; for example, the mesenteric lymph nodes may begin producing proinflammatory cytokines on immune-cell activation (Maes et al., 2013). Maes et al. proposed that this process drives gut-derived inflammation and is responsible for the increase in IgA- and

IgM-mediated immune responses seen in patients with depression. It is possible that these underlying processes could be corrected by supplemented probiotic bacteria, which may correct dysbiosis, lower levels of inflammation, and limit proinflammatory cytokine production (Logan & Katzman, 2005; Naruszewicz, Johansson, Zapolska-Downar, & Bukowska, 2002).

In summary, several mechanisms have been reviewed that explain how gut health can influence immune responses and inflammation, which can then affect mental health. Risk factors for developing dysbiosis include the use of broad-spectrum antibiotics, psychological stress, very clean environments, and a chronically poor diet. Dysbiosis can cause breakdown of the gut's mucosal barrier, which allows for the interaction of bacteria and the immune system with the possibility of inflammatory reactions. Sufficient contact with certain strains of bacteria is necessary for developing a healthy immune system; inflammation can impair this maturation while increasing the likelihood of maladaptive immune responses to toxic elements produced by some bacterial strains normally present in the gut flora. Also, as discussed earlier, inflammation can negatively affect brain function. The association between dysbiosis and inflammatory activation is a robust one, but there are many other potential causative agents for chronic inflammation, including psychological factors (e.g., childhood adversity; Miller & Cole, 2012), environmental toxins, poor diet (e.g., too much proinflammatory omega-6 in relation to too little anti-inflammatory omega-3), and, as explained in the following section, the act of breathing.

Oxidative Stress and Mental Health

In discussions of inflammatory processes, it is essential to consider oxidative stress and to keep in mind that even normal metabolism creates molecules that are proinflammatory. For instance, normal metabolism generates reactive chemical molecules (labeled reactive because they have unpaired electrons) that contain oxygen, often referred to as reactive oxygen species (ROS). The only way to completely eliminate these metabolic products is to cease breathing, but under normal circumstances, we have biological processes that keep them at manageable levels (e.g., production of glutathione, an endogenous antioxidant synthesized throughout the body). Understanding the processes, such as stress, that elevate ROS levels is important, given that ROS can damage cell structures, DNA, RNA, and proteins (cf. Lei et al., 2014, for review). Their potential for harm affects multiple systems: ROS-induced damage can contribute to apoptosis (programmed cell death); neurodegenerative diseases, such as Alzheimer's and Huntington's (Johri & Beal, 2012;

Lopez, Tormo, De Blas, Llinares, & Alom, 2013); and even normal aging (Lau, Shukitt-Hale, & Joseph, 2007).

It is important to recognize that inflammation and oxidative stress are unavoidable components of even the most balanced system. Inflammatory responses are what enable us to fight infection, and they trigger ROS in the process of that fight. As Lei et al. (2014) explained, it is the tightly connected activity of inflammation and ROS generation that modulates some facets of inflammatory activity. Thus, it would be a mistake to categorize inflammation and oxidative stress as necessarily harmful, given that they are essential functions that enable us to maintain health in the face of an infectious agent.

Oxidative stress and ROS-induced damage are also relevant to mental disorders. There are many biomarkers employed as indices of oxidative stress, especially superoxide dismutases (SOD; a group of antioxidant enzymes that detoxify ROS, thus reducing cell damage), nitric oxide activity, and various products of lipid peroxidation (degradation of the lipids contained in cell membranes, which results from electron transfer from the lipids to the toxic free radicals), such as thiobarbituric acidic reactive substances (TBARS). Numerous convincing demonstrations of elevations in SOD and TBARS have been published for many different types of mental disorders, for example, in 35 child and adolescent patients diagnosed with attention-deficit/hyperactivity disorder (ADHD; Ceylan, Sener, Bayraktar, & Kavutcu, 2012), in adults with bipolar disorder (Andreazza et al., 2008), and in patients with paranoid schizophrenia (Dietrich-Muszalska et al., 2012). It is clear from studies of drug-naive patients that the elevated oxidative stress is not necessarily attributable to the use of psychiatric medications (Raffa, Atig, Mhalla, Kerkeni, & Mechri, 2011), and, in fact, it is possible that some medications reduce oxidative stress (Zhang et al., 2012).

Postmortem research has confirmed the association between mental disorders and markers of oxidative stress. A product of lipid peroxidation was evaluated in postmortem tissue in 60 individuals (15 per group) who had been diagnosed with bipolar disorder, major depressive disorder, schizophrenia, or absence of any psychiatric problem (healthy control participants; Wang, Shao, Sun, & Young, 2009). Relative to the healthy control participants, the marker of oxidative stress within the anterior cingulate cortex was significantly elevated by approximately 50% for those patients with bipolar disorder and schizophrenia, although a 33% increase in the 15 patients with major depressive disorder did not reach statistical significance. The next logical question, then, is this: Given that inflammation is influenced by oxidative stress, what controls or influences oxidative stress? For a complete answer to this question, we need to go back several billion years.

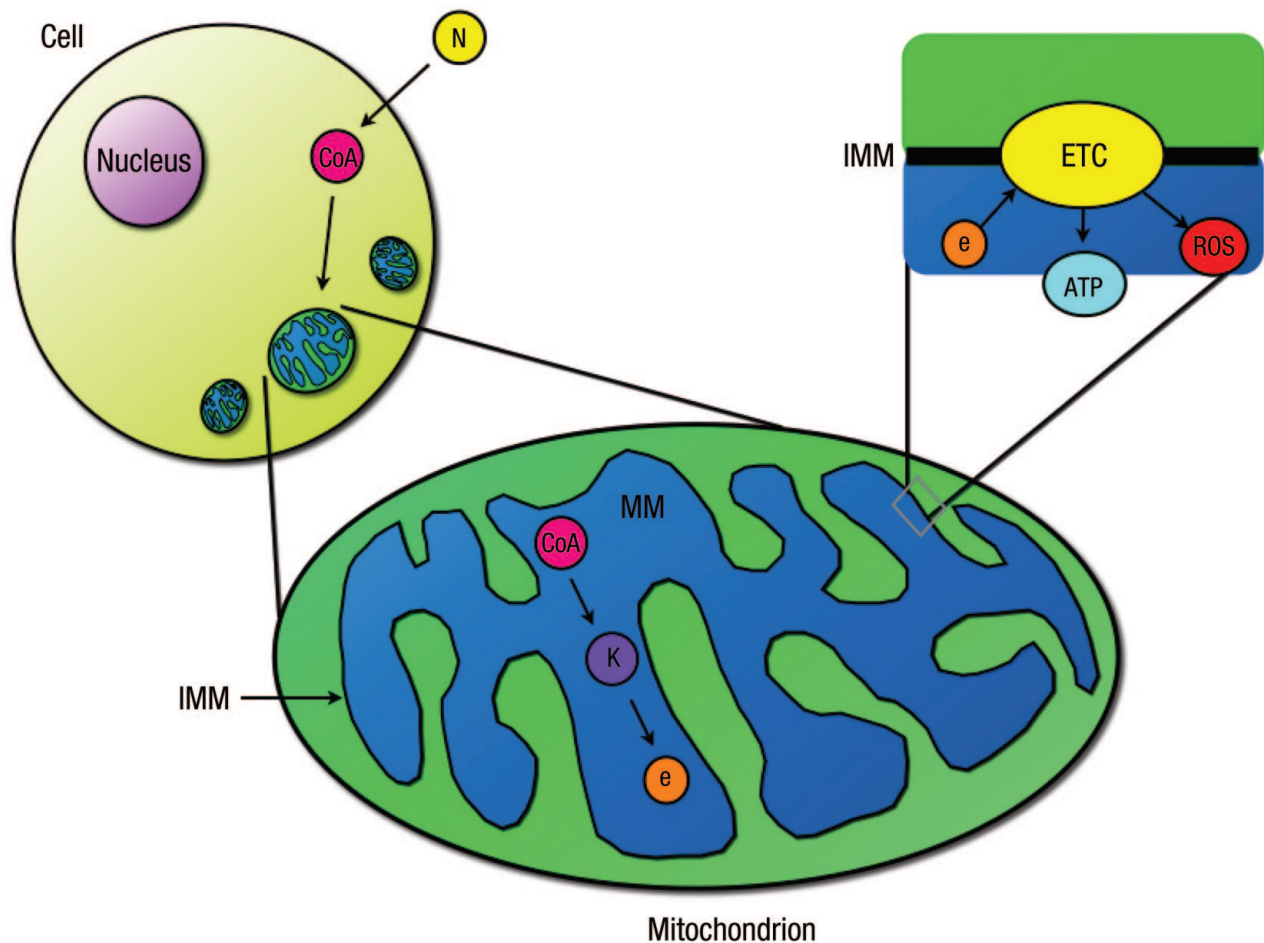


Fig. 1. Schematic illustration of energy generation through the electron transport chain (ETC). Nutrients (N; carbohydrates, fats, proteins) enter the cell and are broken down to acetyl coenzyme-A (acetyl-CoA), which enters the mitochondrial matrix (MM) of the mitochondria. CoA enters the Krebs cycle (K), which liberates electrons (e). Electrons then enter the ETC of the inner mitochondrial membrane (IMM), which generates adenosine triphosphate (ATP) along with reactive oxygen species (ROS).

Mitochondria and Mental Health

Mitochondria are the cellular structures that have evolved in humans to manage inflammation and oxidative stress. Many of us learned in high school about the striated appearance of mitochondria on electron microscopy and about their role as the “powerhouse” of the cell by generating energy in the form of a molecule called adenosine triphosphate (ATP). Billions of years ago, eukaryotic cells (those with membrane-bound nuclei) engulfed primitive mitochondrion-like bacteria, resulting in a “composite” organism with an energy-producing advantage (Karp, 2012). Through millions of years of evolution, these composite cells became complex organisms. All human cells contain multiple mitochondria, which produce ATP using the chemical processes of the Krebs cycle (also known as the citric acid cycle) and the electron transport chain (ETC); also known as oxidative phosphorylation; see Fig. 1 for a schematic illustration of energy generation through the ETC).

The production of ATP is well defined (Karp, 2012). The majority of ATP formation results from products of the Krebs cycle, which occurs in the mitochondrial matrix, the enzyme-rich space within the inner membrane of the mitochondria (see Fig. 1). The Krebs cycle sequentially oxidizes (i.e., removes electrons from) acetyl-CoA, produced from the breakdown of carbohydrates, fats, and proteins. The important products of the Krebs cycle are two high-energy molecules, nicotinamide adenine dinucleotide and flavin adenine dinucleotide (known as NADH and FADH₂, respectively), which receive the electrons from acetyl-CoA.

It is the next step that is being studied particularly in relationship to mental disorders: the ETC. The ETC is embedded in the inner mitochondrial membrane and is made of five enzyme complexes (Karp, 2012). The sequence proceeds this way: NADH and FADH₂, generated previously in the Krebs cycle, donate their electrons to the ETC. These electrons are transferred through a cascade of chemical reactions that create a chemical environment suitable

for the generation of ATP. It is important to note that many cofactors (coenzymes) required for proper enzymatic function in the Krebs cycle and ETC are dependent on the availability of dietary nutrients.

Mitochondrial DNA (mtDNA) and its susceptibility to mutation

When people refer to their genes, they are usually referring to the DNA contained in the nuclei of their cells, nuclear DNA (nDNA). Mitochondria possess their own genome, mtDNA, although it is so small it accounts for only 0.3% of total cellular DNA; the other 99.7% is the nDNA. The mtDNA encodes 13 enzymes involved in the ETC. Ninety-five percent of enzymes present in the ETC, however, are expressed in the nucleus and are shuttled to the mitochondria. Therefore, to characterize mitochondria in a different way, one could say that they are semi-autonomous organelles that are responsible for energy production in the form of ATP, and they have a small (but important) number of coding genes that are distinct from nDNA.

The ETC is efficient at generating energy but requires oxygen to do so. Errors in the reactions involving oxygen are capable of generating the ROS known as superoxide and peroxide. It is important that these ROS can damage mitochondria and cause DNA mutations, and mtDNA is particularly susceptible to ROS-induced damage because of its proximity to the ETC. Furthermore, mtDNA has less efficient DNA repair mechanisms and protective measures than has nDNA, which results in mutations accumulating 10 to 16 times faster than in nDNA (Karp, 2012). The accumulation of mtDNA mutations affects enzyme function in ways that can decrease energy production, thereby causing mitochondrial disease. In other words, it appears that most, if not all, mitochondrial diseases are the result of mtDNA mutations causing a reduction of ATP production. So what are mitochondrial diseases and how might they be relevant to researchers who study mental health?

Mitochondrial diseases

The term *mitochondrial medicine* was coined by Luft in 1994; even at that time, he reported that mitochondrial dysfunction was relevant in more than 100 diseases. Given that all tissues are dependent on the ETC process, and because mitochondria are in all our cells, mitochondrial dysfunction can affect virtually every organ and system in our bodies. As Gardner and Boles (2005) pointed out in their article on “mitochondrial psychiatry,” the most commonly affected tissues are in the brain, ears, eyes, muscle, heart, nerves, endocrine system, GI system, skin, and autonomic nervous system—in other words, almost everywhere. Given the high-energy demands of the brain and the susceptibility of mtDNA to oxidative

stress and mutation, it is not surprising that investigators have proposed mitochondrial dysfunction as a “new” causal pathway to consider in some mental disorders.

Mitochondria and the brain

Although estimates vary, our brains account for only approximately 2% of our body in terms of cellular mass, but they consume at least 20% of the energy our mitochondria generate (Belanger, Allaman, & Magistretti, 2011). So as the biggest energy guzzler in our body, the brain makes huge demands on mitochondrial function. The primary energy demand is for excitatory neurotransmission in the cortex, most of which is mediated by the amino acid glutamate, the most common excitatory neurotransmitter in the human brain.

In contrast to the old dictum that glial cells are the “glue” that holds and supports our neurons, significant breakthroughs in the past decade have revealed that one type of glial cell, known as astrocytes, are essential for sufficient neuronal function. Neurons and glia have comparable numbers of mitochondria, but oxidative metabolism is 10-fold faster in neurons (Belanger et al., 2011), thereby resulting in higher levels of ROS as by-products, which cause oxidative injuries as described earlier. One defense mechanism is the antioxidant ascorbic acid, commonly known as vitamin C. Most plentiful in neurons, ascorbic acid is constantly recycled to manage oxidative stress and likely has a neuroprotective effect (May, 2012). The slower oxidative metabolism found in astrocytes does not mean they are irrelevant to this story. Astrocytes play an important role in the production of another antioxidant, glutathione, thereby providing an additional mechanism to protect neurons from oxidative stress. This is just one example of neuronal dependence on astrocytes, and it is very relevant for the oxidative stress and inflammatory processes already described. For instance, Russell et al. (2006) have developed a model of the pathophysiology of ADHD based on the idea of astrocyte energy deficiency causing impaired and fluctuating task performance in children; they argued that ADHD may be due to low energy metabolism in glial cells.

Overall then, neurons and astrocytes work together to produce energy via their mitochondria and to generate ascorbic acid, glutathione, and other antioxidants to minimize the oxidative damage that would otherwise harm our brains. They do this when their mitochondria work well. But what happens when the mitochondria are impaired?

Some mental disorders may be mitochondrial disorders

Gardner and Boles (2005) proposed a mitochondrial psychiatry model based on defective mitochondrial energy

metabolism's being a predisposing factor in the development of psychiatric disorders. They are not alone in their emphasis on mitochondrial function in mental disorders; for example, the title of a provocative editorial 2 years later asked, "Is Bipolar Disorder a Mitochondrial Disease?" (Young, 2007). And as we discuss later, the evidence of mitochondrial dysfunction in association with mental disorders is increasing.

For example, in a sample of Italian adults (Mancuso et al., 2013) with well-characterized mitochondrial disease, prevalence of psychiatric symptoms was shown to be exceptionally high (approximately 60%) relative to population rates (20%–25%). A neurological comparison group was examined in a report from Hungary in which Inczedy-Farkas et al. (2012) evaluated mental disorders in a group of patients whose mitochondrial mutations had been identified and then compared these patients with people with hereditary sensorimotor neuropathy. The groups were well matched in terms of sociodemographic variables and overall level of disability and on the Somatization subscale of the Symptom Check List-90–Revised. However, results of structured interviews showed that the patients with identified mitochondrial disorders had significantly more depression and anxiety. Of the mitochondrial patients, 47% met criteria for lifetime prevalence of psychiatric disorders, compared with 30% of the neuropathy group. Both of these studies suggested that the psychiatric disturbances may be a direct manifestation of mitochondrial dysfunction and not just a secondary development associated with the distress of illness.

Psychiatry has acknowledged the presence of somatic symptoms in mental disorders for decades, especially since the diagnosis of somatoform disorders appeared in 1980 in the 3rd edition of the *Diagnostic and Statistical Manual of Mental Disorders* (American Psychiatric Association, 1980), but the coexistence of physical and mental problems has rarely been interpreted as a clue regarding etiology. How many clinical psychologists and psychiatrists have been confronted with questions from patients such as, "Why do my legs hurt when I am sad?" It is perhaps of great relevance, then, that higher ATP production in 21 patients with chronic depression and somatic symptoms was correlated with lower severity of their somatic complaints (Gardner & Boles, 2008). In other words, severity of somatic complaints may be a marker of low ATP production and perhaps also the severity of mental symptoms.

The disorder that has been most extensively studied in relationship to mitochondria is autism spectrum disorder (ASD). ASD was first proposed as a mitochondrial disorder in 1998 by Lombard, and there is much research to support the association. In 25 children diagnosed with "mitochondrial autism," many had increased blood levels

of lactate (lactic acidosis), pyruvate (important at the beginning of the Krebs cycle), and alanine (Weissman et al., 2008). When Weissman et al. (2008) scanned mtDNA for mutations and defects, they found that 16 of 25 (64%) patients had mutations in mitochondrial enzyme Complex I, whereas the number of mutations in the remaining mitochondrial enzyme complexes was much lower. These results were replicated and expanded in another study of mitochondrial dysfunction in ASD (Giulivi et al., 2010) that showed impaired function as well as mtDNA errors. A recent systematic review of 12 studies of the relationship between mitochondria and ASD reported that the findings in all the studies provided evidence of both elevated ROS production and impaired ETC function (Ghanizadeh, Berk, Farrashbandi, Alavi Shoushtari, & Villagonzalo, 2013). Frye and Rossignol (2011) summarized the concept well in the title of their review article "Mitochondrial Dysfunction Can Connect the Diverse Medical Symptoms Associated With Autism Spectrum Disorders."

Describing the role of various nutrients in optimizing mitochondrial function is difficult, given that there are those that have direct functions (e.g., both niacin and riboflavin are structural components of cofactors that are critical for ATP production) and also those with an indirect impact on mitochondrial function (e.g., heme deficiency causes mitochondrial decay and oxidative stress, and the production of this form of iron depends on several nutrients, such as vitamin B6, copper, and zinc). When all the steps of cellular metabolism and energy production are combined for consideration, it appears as if virtually all the known minerals, vitamins, amino acids, and essential fatty acids are involved. For that reason, it is logical to consider the topic of using multiple nutrients to optimize mitochondrial function.

Nutrient-Treatment Research

If many emotional symptoms are at least partly a product of inflammation, gut dysbiosis, elevated ROS, and impaired mitochondrial energy production, why are these variables so important for people studying or treating mental disorders? The answer is simple: The mainline treatments of these metabolic challenges can be grounded in lifestyle changes, with nutrients and probiotics leading the way. As discussed by other researchers (Walsh, 2011), clinicians have traditionally underutilized therapeutic lifestyle changes in spite of abundant evidence of their positive therapeutic potential. One of eight therapeutic lifestyle changes reviewed by Walsh (2011) is nutrition, which consists of both food selection and supplements. What follows is a discussion of each of his two subcategories, with particular application to mental health.

Food selection

Although the association between diet and mental health has been investigated for nearly a century (Kaplan, Crawford, Field, & Simpson, 2007), there is a growing body of much more recent research that supports this relationship in a manner that mental-health clinicians could extrapolate into practice (Jacka, Pasco, et al., 2011). Nutritional epidemiology studies of large populations have often reported better mental health in individuals who consume healthier diets (defined variously, but generally including whole foods with lots of fruits, vegetables, and nuts; Jacka, Kremer, et al., 2011). This finding is relevant not only to the general population but also to individuals with already-diagnosed disorders. In a sample of 97 adults with confirmed diagnoses of depression or bipolar disorder, analysis of 3-day food records revealed consistently positive correlations between intake levels of micronutrients (defined as vitamins and minerals; in this case, six vitamins and five minerals) and their Global Assessment of Functioning scores (Davison & Kaplan, 2012).

However, improving dietary intake alone may not be sufficient to affect symptoms for everyone for reasons that go beyond this review (Kaplan et al., 2007) but partly because mitochondrial mutations may cause lowered energy production that may not be fully corrected by improving dietary choices. Some individuals may need nutrient boosts beyond those that can be provided through making better food choices in order to address these limitations.

The following question always arises when discussing nutrition and mental health: Which nutrients do people need to take? If one looks only at the nutrients that are usually defined as “essential” (meaning humans cannot synthesize a sufficient amount of them and must ingest them), many nutrition scientists tend to speak of approximately 40 to 50 (Ames, Elson-Schwab, & Silver, 2002): roughly 15 vitamins, 15 minerals, 10 amino acids, plus the essential fatty acids. But even these estimates cannot be accepted as definitive; there are many phytonutrients in our fruits and vegetables whose role in human health have not yet been fully determined (e.g., the more than 600 carotenoids, such as lutein and lycopene). The one principle that is clear, even without having precise numbers validated scientifically, is that humans have evolved to need a very broad spectrum of nutrients, consumed in balance. Some of those balances are understood and guide manufacturers of supplement formulas that contain multiple nutrients; for example, magnesium helps you absorb calcium, so they are often together in the same formula, and zinc and copper need to be consumed in a particular ratio of approximately 10:1. Other questions about nutrient balance and interaction still need to be defined; for instance, are the phytonutrients that nature

has “packaged” along with the minerals and vitamins in fruits and vegetables acting synergistically and improving absorption/metabolism?

One illustration of how scientists and clinicians sometimes package nutrients together for clinical treatment relates to the classical mitochondrial diseases. Mixes of nutrients (usually referred to as “mitochondrial cocktails”) used to treat physical mitochondrial disorders typically contain B vitamins; the antioxidant vitamins A, C, and E; as well as coenzyme Q10, L-carnitine, and creatine, all aimed at supporting the mitochondrial Krebs cycle and the manufacture of ATP (Gardner & Boles, 2005). In contrast, nutrient treatments for psychiatric illness are not typically framed as treatments for enhancing ATP, although it is very possible that the reported benefits may be due in part to the support these nutrients provide for mitochondrial function.

Research on single-nutrient treatments

There is now a large body of literature on single nutrients for the treatment of psychiatric conditions (Kaplan et al., 2007; Rucklidge & Kaplan, 2013) and a substantial number of studies using a broad spectrum of nutrients. The difference between these two approaches is critical for understanding current developments in nutritional psychiatry/psychology. Historically, and over several centuries, the single-nutrient strategy yielded significant progress in mental health, as seen with such phenomena as myxedema madness (treated with iodine), the mental symptoms of pellagra (caused by deficiency in niacin or nicotinic acid, vitamin B3), psychosis of pernicious anemia (deficiency of cobalamin, vitamin B12), and Wernicke’s encephalopathy (deficiency of thiamine, vitamin B1). There is also a substantial literature base that uses specific mitochondrial cocktail ingredients, such as L-carnitine, to improve mood (Bella, Biondi, Raffaele, & Pennisi, 1990; Cruciani et al., 2006; Malaguarnera et al., 2011; Zanardi & Smeraldi, 2006) and symptoms of ASD (Geier et al., 2011) and to treat, with mixed results, ADHD, with some positive trials (Van Oudheusden & Scholte, 2002) and some negative (Abbasi et al., 2011; Arnold et al., 2007). Creatine has been used successfully to augment the effects of antidepressants (Lyoo et al., 2012) as well as for treatment-resistant depression (Roitman, Green, Osher, Karni, & Levine, 2007). There is some preliminary evidence that coenzyme Q10 can ameliorate bipolar disorder in older patients (Forester et al., 2012), although further replication is necessary.

Research on multinutrient formulas

Although we recognize the promise of these studies that employ a single-nutrient approach, we suggest that this

method has significant limitations because of the nature of brain metabolism. It makes better physiological sense to use a broad selection of nutrients, given that no one ingredient on its own would support all the biochemical reactions necessary for optimal function (Rucklidge, Johnstone, & Kaplan, 2013). With only a few exceptions (Schoenthaler & Bier, 2000; Schoenthaler et al., 1997), the multinutrient-intervention research relevant to mental health has been published in only the brief period since the beginning of this century. Most of this relatively new research has investigated the use of micronutrients in combination (vitamins, minerals, and amino acids usually given in amounts larger than the recommended daily allowance but not considered “mega” doses) as treatment for mental problems. A recent systematic review has shown that there is quite a substantial literature on the use of broad-based formulas for the treatment of symptoms ranging from depression to stress to antisocial behaviors, and, overall, the results across different designs, including randomized controlled trials (RCTs), case studies, case series, case-control studies, and database analyses, are generally positive (Rucklidge & Kaplan, 2013).

For example, in the treatment of antisocial and violent behavior, there have been four RCTs, all of which support the use of broad-based formulas in reducing offending behaviors. Schoenthaler et al. (1997) reported an RCT that resulted in a 28% decrease in rule violations in 62 imprisoned delinquents given a daily micronutrient formula when compared with those who received a placebo. An RCT on delinquent behavior in schoolchildren aged 6 to 12 yielded similar results (Schoenthaler & Bier, 2000): 80 children given a broad-spectrum formula had a 47% lower mean rate of antisocial behavior requiring discipline than did 80 children who received a placebo. In another RCT, there was a 35.1% decrease in disciplinary incidents for 231 young offenders who received a supplement that consisted of 25 vitamins and minerals, plus some essential fatty acids, compared with a reduction of only 6.7% in individuals who received a placebo (Gesch, Hammond, Hampson, Eves, & Crowder, 2002). Partial replication of this result has been reported in a different sample (Zaalberg, Nijman, Bulten, Stroosma, & van der Staak, 2010).

In the area of anxiety and mood, there are many RCTs. Schlebusch et al. (2000) found that compared with participants receiving a placebo, adults given a broad micronutrient formula improved on all psychometric measures of stress during a 30-day RCT. In a 16-week RCT of 114 adults, participants taking a multivitamin under blinded conditions reported significantly better energy levels and mood than did those on placebo (Sarris et al., 2012). A trial of 60 adults with major depressive disorder showed greater reductions on the Beck Depression Inventory for participants who were randomized to receive a B-complex

formula compared with those receiving a placebo (Lewis et al., 2013). In other research, compared with a placebo control group, nonclinical samples who consumed a complex nutrient formula showed improved mood and decreases in anxiety and perceived stress (Kennedy et al., 2010; Stough et al., 2011), although not all trials have documented benefit in nonclinical samples (Cockle, Haller, Kimber, Dawe, & Hindmarch, 2000; Haskell et al., 2008).

Within older populations known for comorbid physical health problems, some trials show additional benefit of nutrients on psychological symptoms. For example, in an RCT with 73 nursing home residents, use of micronutrients was shown to assist with mood in those residents with low levels of selenium (Gosney, Hammond, Shenkin, & Allsup, 2008). In an RCT of a complex micronutrient formula in 225 hospitalized older patients suffering from a variety of acute illnesses, patients who received the active version displayed fewer signs of depression than did those who received a placebo, even if they had not been clinically depressed (Gariballa & Forster, 2007). In other words, there was evidence of improved mood in everyone receiving the micronutrients—individuals with severe or mild depression, as well as those not previously reporting low mood.

One 36-ingredient micronutrient formula, consisting mainly of minerals, vitamins, and amino acids, has been researched for the treatment of bipolar disorder across both adults and children (e.g., Gately & Kaplan, 2009; Kaplan et al., 2001; Rucklidge, Gately, & Kaplan, 2010). In all reports, the effects of this formula have been positive. In five open-label series, children and adults with bipolar disorder or bipolar symptoms improved significantly, sometimes within a few days of commencing the formula (Rucklidge & Kaplan, 2013). All five trials showed significant change sustained over at least a 6-month period, with approximately 70% to 80% of participants showing much or very much improved bipolar symptoms and a reduction in the amount of medications required to maintain symptom control. Furthermore, in a database analysis of a large sample of 358 adults with bipolar disorder, more than half were positive responders (defined as more than 50% decrease in symptom severity) after 3 months of consumption of this micronutrient formula (Gately & Kaplan, 2009). It is important that their symptom improvement was sustained at 6 months, thereby making it unlikely that placebo or expectancy effects accounted for the reported changes. These findings were replicated in a similar database analysis of 120 children and adolescents with bipolar disorder (Rucklidge et al., 2010). Of note, effect sizes for primary outcome measures are large (more than 0.8) across all these reports, and results have been replicated by investigators in multiple settings in three different countries.

Results from case studies have been consistent with group data. Some of the case studies documented remission of pediatric psychosis (Rodway et al., 2012); others showed on-off control of symptoms depending on the presence or absence of the nutrient formula and long-term maintenance of benefit (Kaplan et al., 2002). Part of the value of the case studies is that they provided empirical evidence of symptom remission that was sustained for at least 4 years (Kaplan et al., 2002; Rodway et al., 2012) and could be compared with a clinically documented history of 6 years of extensive conventional treatment (Frazier, Fristad, & Arnold, 2009). Overall, the lack of RCTs with a placebo control makes this micronutrient treatment less appealing to many; however, the consistency of findings across universities and countries indicates it is a worthy option for more rigorous trials.

In the area of neurodevelopmental disorders, such as ASD and ADHD, there have been positive open-label trials (e.g., Rucklidge, Taylor, & Whitehead, 2011), case-controlled studies (Mehl-Madrona, Leung, Kennedy, Paul, & Kaplan, 2010), and RCTs (Adams et al., 2011; Katz, Levine, Kol-Degani, & Kav-Venaki, 2010; Rucklidge, Frampton, Gorman, & Boggis, 2014a) with various formulas. For instance, Katz et al. (2010) compared an herbal supplement containing micronutrients with a placebo in ADHD children; compared with the placebo group, those children taking the active ingredients for 4 months showed significantly greater improvements on the Test of Variables of Attention. Adams et al. (2011) studied 141 children and adults with ASD by comparing nutrients with placebo and found that the supplemented group had greater improvements than did the placebo group on the Parent Global Impressions–Revised and subscales of Hyperactivity, Tantrums, and Receptive Language. Rucklidge et al. (2014a) studied 80 adults with ADHD and compared micronutrients with a placebo; they documented superiority of nutrients in the treatment of ADHD symptoms as well as other areas of psychological functioning. For individuals who stayed on the nutrients, these changes were maintained at 1-year follow-up (Rucklidge, Frampton, Gorman, & Boggis, 2014b).

In the treatment of addictions, Blum and colleagues have developed formulas they refer to as “neuroadaptagens” or “neuronutrients” that consist mainly of amino acids, although some earlier formulas contained minerals and vitamins (see Chen et al., 2011, for a review). This line of research supports the use of nutrients to reduce relapse rates (Blum, Chen, & Chen, 2009; Brown, Blum, & Trachtenberg, 1990; Guenther, 1983), reduce drug hunger and withdrawal (Blum, Allison, Trachtenberg, Williams, & Loeblich, 1988; Harrison, Rucklidge, & Blampied, 2013), and improve psychological functioning (Poulos, 1981). Given that no researchers have investigated a causal pathway to date, at this point, we can only

speculate that nutrients reduce inflammation related to drug intake and drug withdrawal and may also provide the mitochondria with additional nutrients to function.

There is compelling reason to consider the public-health implications of supplementation with broad-spectrum formulas that include both minerals and vitamins. One case-control study in which researchers compared people taking nutrients with those not taking nutrients at the time of an earthquake, and also one RCT that used different doses of micronutrients after an earthquake, showed that supplementation improved resistance to stress (Rucklidge et al., 2012; Rucklidge, Johnstone, Harrison, & Boggis, 2011), and these changes were maintained 1 year later (Rucklidge, Blampied, Gorman, Gordon, & Sole, 2014). Given that micronutrients support the energy output of mitochondria and provide protection from oxidative stress in the form of antioxidants, it is plausible that they help people cope with the harmful effects of stressors, which indicates the value to public health of having a well-nourished populace. A very inexpensive public-health initiative would be to incorporate micronutrient supplements into every disaster relief effort.

There is also a compelling financial reason to consider expanding the use of broad-spectrum nutrient formulas: They are much less expensive than many conventional treatments of mental disorders. In one case report of a child with severe psychosis and obsessive compulsive disorder, 6 months of treatment with a broad-spectrum mineral and vitamin formula cost less than 1% of the cost of the previous 6 months of inpatient care in a specialized tertiary care hospital (Rodway et al., 2012). There was also a big difference in treatment benefit: There was no symptom amelioration from expensive inpatient care, but all symptoms resolved with micronutrient treatment. Prevention of mental-health problems caused by crises or natural disasters could potentially save millions of dollars of mental-health treatment costs. And a few hundred dollars of minerals and vitamins may be a significant savings relative to the costs of psychiatric treatment and the social costs of family distress; this latter point, however, requires much additional research. And given the rapidly rising cost of mental-health care to society, there is a social imperative to investigate this approach more thoroughly.

It is important to note that nutrient intake is not necessarily a perfect predictor of nutrient availability. As mentioned previously, the microbiome plays many important roles in digestion, including harvesting otherwise inaccessible nutrients from our food and synthesizing vitamins. A damaged population of protective bacteria can lead to increased permeability of the gut wall, which also impairs nutrient absorption (Holzapfel, Haberer, Snel, & Schillinger, 1998). This information leads logically to the consideration of nutrient treatment that includes

probiotics. Treating with a combination of probiotics (either through dietary means, such as yogurts or fermented foods, or with formulated probiotic supplements) alongside micronutrients may have an advantage of ensuring that nutrient absorption is maximized.

In summary, although nutrient treatments have not typically been designed to target the mitochondria or inflammation, the ingredients certainly suggest that the nutrient formulas likely have an impact on these pathways, and the findings are consistent with the studies reviewed herein showing relationships between mental and mitochondrial disorders. Gut dysbiosis is extremely common in our modern society, so the correction of bacterial imbalances may provide a key element to improving the efficacy of nutrient supplementation. As discussed later, one of the most urgent needs for further trials is the examination of micronutrients for the treatment of psychiatric illness but with the inclusion of measures of oxidative stress and mitochondrial function.

Conclusion: The Future

The mechanisms reviewed in this article constitute a new model for understanding the etiology of the symptoms of mental disorders.¹ In a healthy person with a healthy GI system, who eats a healthy diet and absorbs nutrients efficiently, there is usually sufficient nutrient availability for mitochondria to function optimally and produce adequate amounts of ATP to deal with the stresses of life. Our ATP provides a natural defense against the oxidative stress that occurs from normal metabolism and can help heal a compromised GI system. Our ATP also helps protect us from many environmental toxins and stressful life events. When clients understand this simple sequence, eating optimally to feed their mitochondria is likely to make sense.

A bright new future of understanding, preventing, and treating mental disorders awaits us, and these advances surprisingly will return us to what our ancestors knew and accepted a century ago. In the early 20th century, when prairie and western homesteaders anywhere in North America needed information about the health of their families or livestock, they turned to the three-volume *People's Home Library*, in which the volume called *The People's Home Medical Book* states clearly that insanity is caused by "imperfect nutrition" (Ritter, 1910, p. 209). Now, in the early 21st century, we are beginning to understand why. In our current scientific era, it is essential that the mechanisms be understood to successfully shift the scientific paradigm from a primarily pharmacologic model of mental-health treatment to nutritional medicine, and understanding those mechanisms requires much more research.

We propose two types of research to expand knowledge of this area: (a) relatively simple addition of

measures to ongoing studies to answer questions about etiology, and (b) evaluation of the incremental benefit of nutrient treatment in follow-up extensions.

Addition of measures

As mentioned earlier, nutrient-treatment studies urgently need to quantify biomarkers of oxidative stress and mitochondrial function. The same can be said of the epidemiologic studies that currently rely primarily on surveys. Only a few years ago, these assays were very challenging, and there is still controversy about whether peripheral measures of mitochondrial function adequately reflect brain metabolism. But in the absence of brain biopsies, they will have to suffice for the moment, and clinical scientists evaluating nutrition and diet in relation to mental health need to incorporate as many of these measures as possible. Of course, these assays can be expensive, so educating the major funding agencies about the importance of this topic is another facet to consider.

A second type of measurement "add-on" that could be quite fruitful involves the investigation of physiological processes that may account for comorbidity of physical and mental symptoms. For years, an association between depression and cardiovascular disease has been noted and usually attributed to the fact that feeling ill with heart disease makes people feel scared and sad. Although there is likely much truth to that attribution, recently scientists have begun to entertain the idea that there might be some underlying relevant physiological pathways affecting both systems. The autonomic nervous system, HPA axis, and inflammatory cytokines are all being considered now as playing a role in the development of both depression and heart disease (Fiedorowicz, 2014). Given that the brain and heart are the two most metabolically demanding organs in terms of mitochondrial function and ATP use, it seems somewhat logical to investigate this issue, especially because people with both disorders (mental and cardiovascular) are at particularly high risk of death. Adding measures of depression as well as biomarkers of mitochondrial function to many more of the ongoing studies of heart health would enrich our knowledge of this topic.

Finally, in all these studies, we encourage scientists to engage the assistance of a health economist. The cost of mental-health treatments is an important societal issue, and if some of the treatment approaches just mentioned are less expensive than conventional medication, researchers ought to be demonstrating that. As mentioned earlier, so far, there seems to be only one case study in which health-care costs of 6 months' inpatient care were compared with 6 months' outpatient treatment with micronutrients (Rodway et al., 2012). Much more information is needed.

Evaluating the incremental benefit of adding micronutrients

In an Australian study, O'Neil et al. (2013) recently have begun to test the hypothesis that intensive dietary education can affect mental health. Adults with major depression are being randomized to receive either dietary education or social support, and the primary outcome measure is level of depression at 3 months. This is an important study, given that it is difficult to envision placing everyone on earth on nutrient supplements. But we think that an equally valuable question should be addressed as follow-up: Is there any incremental benefit of adding micronutrient supplementation to the two treatments after the end of the 3-month trial? The answer to this question might lead to further questions regarding the ability to detect a priori what factors characterize the people who display an unusually high need for micronutrients, something well known in the physical world (Ames et al., 2002).

Another example of where incremental benefit could be investigated involves research on probiotics. Interest in the gut microbiota and the gut-brain axis is growing at a rapid rate, with many recent narrative reviews having suggested the possible benefits of probiotics alone for mental health (e.g., Basted, Logan, & Selhub, 2013; Cryan & Dinan, 2012). An interesting question, which could be addressed as an additional arm of nutrient research, is do probiotics improve outcomes when given alongside nutrient treatment or dietary education? It is possible that the results of nutrient and diet studies are fundamentally limited by widespread dysbiosis, which may inhibit nutrient absorption, and that adding probiotic treatment could enhance the benefits already seen in nutrient research.

There is excellent research now on the benefits of psychological therapies, such as cognitive-behavioral therapies; the newer third-wave approaches, such as mindfulness, acceptance, and commitment therapy; and meta-cognitive therapy for treatment of a range of psychological problems from depression to anxiety to personality disorders. It is important to determine whether participants who are maximally nourished can optimize their benefit from these therapies. Again, an add-on extension could be used to test the incremental benefit of adding micronutrients for individuals who show benefit initially from the psychological therapy alone. In addition, comparison studies could be conducted to determine whether the combination is more powerful than either nutrients or psychotherapy on their own. A final example involves the very active research field of exercise, yoga, and meditation as treatments for depression. Very few of these studies report changes in biomarkers, but one wonders whether improved brain blood flow (often hypothesized to account for some of the improvements) might be efficacious because of

increased perfusion of the brain with micronutrients absorbed by the gut. The adult brain is perfused by approximately a liter of blood every minute the heart is beating. That liter brings oxygen and carries away waste products, but it also carries the nutrients that humans consume and absorb. An important contribution to science could be made by evaluating the incremental effect of micronutrients added to exercise in terms of mental-health outcomes.

In this review, we have endeavored to engage mental-health researchers and clinicians in exploring a new, exciting model: nutritional mental health. There is now a wealth of research that has demonstrated the importance of inflammation, gut dysbiosis, oxidative stress, and mitochondrial dysfunction for mental health. The nutritional research reviewed herein justifies treating patients through either improved diet or supplementation (or both), given that such treatments could well have beneficial effects on all of these variables. There is a compelling need to foster further research on the topics we have covered, but there is already sufficient knowledge available to influence clinical practice. Mental-health clinicians are well poised to engage clients in understanding the importance of lifestyle changes in addressing psychological issues. This article provides both researchers and clinicians with a 21st-century framework within which such recommendations can be considered.

Author Contributions

B. J. Kaplan drafted the manuscript and takes responsibility for all final information; J. J. Rucklidge, A. Romijn, and K. McLeod wrote individual sections and edited the final version; K. McLeod created the figure.

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The authors declared that they had no conflicts of interest with respect to their authorship or the publication of this article.

Note

1. A new scientific society was formed in the summer of 2013: the International Society for Nutritional Psychiatry Research (ISNPR). As of this writing, the scope of ISNPR's activities is not yet clear—whether it will include a new scientific journal, an independent annual meeting, and so on. But we mention this watershed development because the scientists participating in this new venture represent each of the various topics covered in this review. Drawing mental-health scientists from all over the world, ISNPR consists of researchers publishing correlational and observational studies (e.g., nutritional epidemiology), inflammation and oxidative stress research, studies of the microbiome and dysbiosis, mitochondrial research, and clinical

studies of dietary modification and nutrient treatment. The evolution of ISNPR will stimulate many future studies and collaborations on these topics. References to new studies appearing on these topics can be found at ISNPR.org. The position statement of ISNPR is in press for *Lancet Psychiatry*.

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