Nutritional psychiatry

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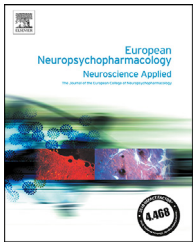

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REVIEW

Nutritional psychiatry: Towards improving mental health by what you eat

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Abstract
Does it matter what we eat for our mental health? Accumulating data suggests that this may indeed be the case and that diet and nutrition are not only critical for human physiology and body composition, but also have significant effects on mood and mental wellbeing. While the determining factors of mental health are complex, increasing evidence indicates a strong association between a poor diet and the exacerbation of mood disorders, including anxiety and depression, as well as other neuropsychiatric conditions. There are common beliefs about the health effects of certain foods that are not supported by solid evidence and the scientific evidence demonstrating the unequivocal link between nutrition and mental health is only

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beginning to emerge. Current epidemiological data on nutrition and mental health do not provide information about causality or underlying mechanisms. Future studies should focus on elucidating mechanism. Randomized controlled trials should be of high quality, adequately powered and geared towards the advancement of knowledge from population-based observations towards personalized nutrition. Here, we provide an overview of the emerging field of nutritional psychiatry, exploring the scientific evidence exemplifying the importance of a well-balanced diet for mental health. We conclude that an experimental medicine approach and a mechanistic understanding is required to provide solid evidence on which future policies on diet and nutrition for mental health can be based.

1. The limited scientific evidence base for nutritional advice on mental health

Information in the popular press about the link between nutrition and mental health is increasingly invading our daily lives, whether the goal is to improve mood, enhance cognitive function, prevent its decline, or even provide beneficial effects in certain brain diseases, including neuropsychiatric conditions such as epilepsy, attention deficit hyperactivity disorder (ADHD) and autism.

There appears to be a general belief that dietary advice for mental health is framed around a solid scientific evidence base. In reality, for many such claims, it is very difficult to prove that specific diets or specific dietary components contribute to mental health either by causing, preventing or treating disease.

Neuropsychiatric disorders represent some of the most pressing societal challenges of our time, and all data show that the burden of mood-disorders, stress-induced cognitive vulnerabilities and psychiatric disorders will continue to rise in Europe and globally over the coming decades. Effective preventative strategies are of critical importance to the public health domain. Research on diet as a crucial contributing determinant to mental health, while difficult to perform and hard to interpret, is urgently needed.

The composition, structure and function of the brain are dependent on the availability of appropriate nutrients, including lipids, amino acids, vitamins and minerals (Castro et al., 2018; Delpech et al., 2015b; Lepinay et al., 2015). It is therefore logical that food intake and food quality would have an impact on brain function, which makes diet a modifiable variable to target mental health, mood and cognitive performance (de la Torre et al., 2016; Dinan et al., 2018). In addition, endogenous gut hormones, neuropeptides, neurotransmitters, and the gut microbiota, are affected directly by the composition of the diet (El Aidy et al., 2015; Sandhu et al., 2017; Schellekens et al., 2012; Torres-Fuentes et al., 2017; van de Wouw et al., 2017).

Cross-sectional population-based epidemiological studies can provide information on nutrients and diets that are associated with mental health and disease, but they do not demonstrate cause, benefit or remedy. With some notable exceptions, properly controlled dietary intervention studies of sufficient duration and specificity that demonstrate beneficial effects for mental health are lacking. Intervention studies are often limited methodologically due to small sample sizes, heterogeneity within the samples, lack of biomarkers to adequately stratify within and across populations, difficulties in blinding participants to the nature of a nutritional intervention and a lack of randomized allocation to treatment conditions and/or a lack of blinded observers. In general, the small effect sizes of nutritional interventions in healthy adults may render their detection difficult. However, we have reason for optimism, as under conditions of impaired functioning or disease, the effects of nutritional interventions could be substantial. Specific nutritional needs under disease conditions or specific nutrient deficiencies (or excess) in the diet may contribute to disease progression or severity or trigger disease development. The emergence of the new research field "*Nutritional Psychiatry*" (Sarris et al., 2015a) offers promise in identifying which dietary components are truly important for mental health, including in psychiatric disease, as well as to whom, under which circumstances and at which specific dosages these nutritional interventions have preventative and therapeutic efficacy.

2. Evidence from meta-analyses that food affects mental health

Scientific findings demonstrating the unequivocal link between nutrition and mental health are only beginning to emerge. Nevertheless, several studies have reported strong correlations between a healthy diet and mental well-being, which can help to inform future recommendations on diet (Dinan et al., 2018). For example, increased consumption of a diet rich in fresh fruits and vegetables has been associated with increased reported happiness and higher levels of mental health and well-being (Conner et al., 2017; Emerson and Carbert, 2019; Fresan et al., 2019; Moreno-Agostino et al., 2019; Mujcic and Oswald, 2016).

There have been several systematic reviews and meta-analyses exploring the relationship between nutrition and mental health. For example, an analysis of four cohorts and nine cross-sectional studies, showed that a reduced likelihood of depression was associated with increased intake of a 'healthy diet', defined as a diet high in fruit, vegetables, fish and whole grains (Lai et al., 2014). The second meta-analysis, consisting of eight cohort studies and one case control, linked a reduced risk of depression with adherence to the Mediterranean diet (Psaltopoulou et al., 2013). More

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recently, a systematic review combining a total of 20 longitudinal and 21 cross-sectional studies, provided compelling evidence that a Mediterranean diet can confer a protective effect against depression (Lassale et al., 2018). In addition, a meta-analysis of 16 randomized controlled trials also indicated that dietary interventions hold promise to reduce depression incidence (Firth et al., 2019). In contrast, a recent meta-analysis of cohort studies revealed no significant association between adherence to the Mediterranean diet and risk of depression (Shafiei et al., 2019). However, when cross-sectional studies were analyzed an inverse significant association was found between depression odds and the adherence to the Mediterranean diet. Together, these studies provide a reasonable evidence base to further investigate the effect of specific dietary interventions on mental health.

3. Deficiencies in vitamins and disease-specific diets impacting on mental health

A prominent example of a dietary intervention that affects brain health is the ketogenic diet for children with epilepsy (Neal et al., 2008). In this example, the mechanism is unknown, but the reduced epileptic seizures under fasting conditions, when ketone bodies provide the energy for the brain, suggest that an altered energy supply may be instrumental (Morris, 2005). Phenylketonurea is another example for which an elimination diet prevents cognitive decline (Borghi et al., 2019). In addition, studies have shown that deficiencies of various nutrients, primarily vitamins, impair cognition (Gaudio et al., 2016; Giannunzio et al., 2018). The link is strongest for vitamin B12 (its deficiency causes fatigue, lethargy, depression, poor memory and is associated with mania and psychosis) (Smith et al., 2018; Tangney et al., 2011), thiamine (vitamin B1; its deficiency causes beriberi with numbness as CNS symptom and Wernicke's encephalopathy), folic acid (vitamin B9; its deficiency has detrimental effects on neurodevelopment in utero and in infancy; and deficits are associated with a greater risk of depression during adulthood (Black, 2008; Enderami et al., 2018), and niacin (vitamin B3; its deficiency causes Pellagra with dementia as a result) (Hegyi et al., 2004). Yet even for these deficiencies, the role of mild "subclinical" or multiple mild deficiencies in the genesis of mental dysfunction is unclear. For example, the effect of vitamin D on mental health has been assessed in several trials with conflicting results. Higher serum vitamin D concentrations have been associated with better attention and working memory performance in community-dwelling older adults, aged 65 years and older (Brouwer-Brolsma et al., 2015). Throughout childhood, adolescence and adulthood randomized controlled trials (RCTs) have – albeit not uniformly - provided evidence for an effect of vitamin D supplementation on depression (Focker et al., 2017); an effect on attention deficit/hyperactivity disorder has also been suggested (Mohammadpour et al., 2018). Based on cutoffs derived from assessment of bone health, a substantial proportion of the general population has a vitamin D deficiency, which underscores the necessity of providing conclusive evidence for its efficacy in neuropsychiatric disorders. A healthy diet, rich in polyphenols, and polyunsaturated fatty acids (PUFAs) and nutritional supplements including vitamins, has been reported to exert favorable effects on mental health, including on cognitive performance, mood, stress reactivity and neuroinflammation (Bazinet and Laye, 2014; Firth et al., 2018; McGrattan et al., 2019; Pusceddu et al., 2015; Rapaport et al., 2016),particularly in conditions associated with high levels of inflammation e.g. liver diseases (Su et al., 2014) and in older adults (Delpech et al., 2015a, 2015c; Labrousse et al., 2012; Larrieu et al., 2014; Lepinay et al., 2015; Zamroziewicz et al., 2017).

4. Diets for ADHD and autism

Several dietary interventions have been studied in ADHD. A meta-analysis across 20 studies including 794 participants found a small effect size of elimination of food additives based on parent reports, 0.18, that however decreased to 0.12 when taking into account possible publication bias (Nigg et al., 2012). Also, more rigorous elimination diets have been shown to be effective in several randomized clinical trials. Two independent meta-analyses reported effect sizes of 0.29 to 0.51 across 6 controlled trials (Nigg et al., 2012; Sonuga-Barke et al., 2013), and concluded that approximately one third of the children with ADHD were responsive (>40% symptom reduction) (Nigg et al., 2012). Supplementation of free fatty acids has also been associated with a small but reliable reduction of ADHD symptoms, with effect sizes varying from 0.18 to 0.31, according to meta-analyses (Bloch and Qawasmi, 2011; Sonuga-Barke et al., 2013). Supplementation with micronutrients (i.e. vitamins and minerals) has been associated with less aggression and better emotion-regulation in children with ADHD (Rucklidge et al., 2018). Moreover, a recent meta-analysis suggested that a diet high in refined sugar and saturated fat may manifest an increased risk for ADHD or hyperactivity, in contrast to the potential protective effect of a diet high in fruits and vegetables (Del-Ponte et al., 2019). Nevertheless, it was also highlighted that the low number of the studies available in the literature together with design limitations weaken the current evidence and longitudinal studies need to be performed going forward. Results of nutritional interventions (ranging from supplementation with vitamin D and micronutrients to gluten-free and casein-free) in autism are also very diverse, and have not been subjected to rigorous meta-analyses. Thus, particularly in autism, better controlled studies are required and multiple mechanisms may explain efficacy (Ly et al., 2017).

5. Towards diets for mental health

Overall, there is a paucity of RCTs investigating the effectiveness of dietary change in the treatment of mental health. One of the first intervention studies performed to date, involved a 12 week Mediterranean diet. Significant improvements in mood and reduced anxiety levels in adults with major depression were reported (Jacka et al., 2018, 2017). More recent RCTs confirmed the benefits of Mediterranean-style diet on mental health in depression, namely the HELFIMED (Parletta et al., 2019) and PREDI_DEP

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(Sanchez-Villegas et al., 2019) trials. In contrast, multinutrient supplementation in the MooDFOOD RCT did not reduce episodes of major depression in overweight or obese adults with subsyndromal depressive symptoms (Berk and Jacka, 2019; Bot et al., 2019). This highlights that advance nutritional psychiatry, it will be important to replicate, refine and scale-up dietary intervention studies aimed at prevention and treatment of common disorders of mental health. In addition, there is an unmet need for more randomized controlled clinical trials. Collectively, the aforementioned clinical trials provide specific examples for which it is possible to alter brain function and mental health by specific dietary interventions. An important future step will be to discover the metabolic and cellular processes that connect nutrition to brain function in health and in disease. We also need to establish whether specific nutrients or dietary patterns of whole foods have beneficial effects on mental health (Gibson-Smith et al., 2019). Experimental medicine approaches can also help to assess effects of dietary interventions; in order to optimize our selection of nutrients/diets to be tested in expensive and lengthy interventions, we must make the best use of current knowledge including the choice of appropriate biomarkers.

6. Diet, mental health and cognition across the lifespan

Early life development sets the stage for later development and may influence individual susceptibility for disease. Therefore, a personalization of nutrition for mental health should take early life development into account. Any effects of nutritional intervention during the period of early brain growth (the so-called first 1000 days, e.g. from conception until 2 years of age) may have a larger impact on later health than do interventions later in life. Progress will also be made through increasing fundamental understanding of how nutrients affect signaling processes that are important for brain function, such as metabolic, endocrine, and immune and other signaling processes, including those that act via the gut microbiota (Dinan et al., 2018; Fernandez-Real et al., 2015; Wang et al., 2018b).

In newborn humans, the brain represents about 13% of lean body weight and its further growth and development is subject to both energetic and nutritional constraints (Cunnane and Crawford, 2014). Reliable access to an adequate dietary supply during this period of rapid growth is essential. To date, a major focus in the area of nutritional psychiatry has been on the cognitive impairments evoked by early-life malnutrition (Innis, 2008; Laus et al., 2011; McNamara and Carlson, 2006; Prado and Dewey, 2014; Schwarzenberg and Georgieff, 2018). Early-life nutrition in rodents and humans has been shown to affect cognitive function later in life (Ahmed et al., 2014; Bhutta et al., 2017; de Groot et al., 2011; Dimov et al., 2019; Esteban-Gonzalo et al., 2019; Innis, 2008; Laus et al., 2011; Lumey et al., 2011; Mallorqui-Bague et al., 2018; McNamara and Carlson, 2006; Novak et al., 2008; Prado and Dewey, 2014; Pusceddu et al., 2015; Roy et al., 2012). In addition, vulnerable groups at increased risk for neurological impairment such as preterm born infants or small for gestational age (SGA) infants born term (Castanys-Munoz et al., 2017; Ong et al., 2015), support a direct link between nutritional status and the risk for neurological impairments.

Although all nutrients are necessary for brain growth, key nutrients that support neurodevelopment include protein, iron, choline, folate, iodine, vitamins A, D, B6, and B12 and long-chain polyunsaturated fatty acids (Georgieff et al., 2018). Experimental studies show that the cyto-architecture of the cerebral cortex can be irreversibly disturbed in iodine deficiency during fetal development causing abnormal neuron migratory patterns which are associated with cognitive impairment in children. Iron deficiency anemia during infancy has been shown to be associated with alterations in brain connectivity (Velasco et al., 2018) although the opposite has also been shown to occur (Blasco et al., 2017). Also, more subtle changes in the diet could impact upon early brain development (Algarin et al., 2017). Lipids, and more specifically the omega 3- and 6-polyunsaturated fatty acids DHA (docosahexaenoic acid) and ARA (arachidonic acid) are provided by breast milk, but their levels in breast milk are affected by dietary intake of the mother (Oosting et al., 2015). Studies in mice showed that a diet either enriched in omega-3 fatty acids or with a decreased omega-6 fatty acid levels positively impacted the incorporation of omega-3 fatty acids in neuronal membranes (Freedman et al., 2018; Schipper et al., 2016). Such a low omega-6 diet has recently also shown to completely abolish early life stress induced cognitive impairments in adult mice (Yam et al., 2019). A recent study demonstrated an improvement in cognitive behaviors and plasticity markers in the brain of adolescence in rats following psychological stress when exposed to a diet enriched with the omega-3 polyunsaturated fatty acids, eicosapentaenoic acid, docosahexaenoic acid, and docosapentaenoic acid and vitamin A (Provensi et al., 2019).

Using a rat maternal separation model, the long-term effects of early-life stress were alleviated by a dietary intervention of milk fat globule membrane (MFGM) and a polydextrose/galacto-oligosaccharide prebiotic blend (O'Mahony et al., 2019).

These findings highlight the important role of a balanced diet in providing an adequate nutrient supply to support brain development for later cognitive function and the relevance of early life development in the vulnerability for (later) psychiatric disease, which may explain, at least in part, the observed heterogeneity in treatment effects.

7. Diet, mental health and cognition in adulthood and later life

A higher diet quality in adult life has been associated with a reduced risk of cognitive decline (Smyth et al., 2015). Moreover, the intake of antioxidant polyphenols in the elderly has been associated with improved cognitive abilities (Anton et al., 2014; Valls-Pedret et al., 2012; Witte et al., 2014). Another study showed that a Mediterranean diet supplemented with olive oil and nuts was associated with improved cognitive function in an older population (Valls-Pedret et al., 2015). A promising role is now emerging for nutritional interventions to combat cognitive decline especially in aging and under conditions of heightened stress and anxiety. Since both increased perceived levels of stress in modern day life and the increasing aging population rep-

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resent major pervasive societal challenges, the potential of nutrition to exert beneficial effects on mental health in both clinical and non-clinical populations should be further investigated (Wu et al., 2016).

In contrast, unbalanced diets increase the risk of cardiometabolic disease and cognitive decline. Thus, it is becoming clear that the negative consequences of a poor-quality diet can impair mental health and cognitive function, which is likely to be exacerbated with age (Agrawal and Gomez-Pinilla, 2012; Prenderville et al., 2015). Interestingly, nutrition and, in particular, malnutrition and obesity, are closely intertwined with mood regulation and stress sensitivity, suggesting a strong link between diet, metabolism and mental wellbeing (Dallman, 2010; Gibson, 2006; Oliver and Wardle, 1999). In addition, a recent cross-sectional analysis showed that the association between depressive symptoms and metabolic syndrome may be partly attributed to physical activity (Matta et al., 2019). Moreover, evidence from rodent models suggests that the consumption of a high fat diet can have anti-depressant and anxiolytic effects (Finger et al., 2011; Leffa et al., 2015). However, there is also evidence from both human and rodent models that a high fat/high sugar western style diet is associated with cognitive impairments, particularly memory impairments (Attuquayefio et al., 2017; Kanoski et al., 2007) and increased anxiety-like behavior (Peris-Sampedro et al., 2019). Furthermore, obesity is associated with hippocampal dysfunction and episodic memory deficits in humans (Cheke et al., 2016; Higgs and Spetter, 2018) and studies in rodents have also linked obesity with hippocampal dependent cognitive impairment (Farr et al., 2008; Heyward et al., 2012; Porter et al., 2013). Thus, a strategy to cope with stress appears to involve increased consumption of a high fat diet, as it has antidepressant and anxiolytic effects, but such a diet in the longer term carries the risk of becoming obese which, in turn, is associated with decreased cognitive functioning and mood disorders.

Clear associations between diet and cognitive and mental health in adulthood have been established but at present we lack a detailed understanding of the metabolic and cellular mechanisms that underpin these associations.

Nutritional interventions could be helpful in reducing the impact of aging and stress on cognitive and mental health but there have been few randomized controlled trials to date, especially in clinical groups.

8. The importance of the microbiome

Recent evidence has highlighted a role for the intestinal microbiome as a key link between the gut and development and function of the brain (Blasco et al., 2017; Dinan and Cryan, 2012; Dinan et al., 2015; Fernandez-Real et al., 2015; Sarkar et al., 2018). Specifically, increasing evidence points to a critical interaction between microbiota in prenatal and postnatal environments and the risk for psychiatric disorders later in life (Codagnone et al., 2019). Moreover, accumulating data has identified the gut microbiota as a key player in the responses to stress and affective disorders, including anxiety, depression and cognition (Bastiaanssen et al., 2019; Cryan and Dinan, 2012; Dinan and Cryan, 2012; Morkl et al., 2018; Noble et al., 2017; Silva et al., 2012). The importance of a healthy gut microbiota in the regulation of serotonin metabolism has also been suggested (O'Mahony et al., 2015). An involvement of the gut microbiome in other disorders such as ADHD, autism spectrum disorders and anorexia nervosa also appears possible (Cenit et al., 2017; Herpertz-Dahlmann et al., 2017; Ly et al., 2017). In addition, stress can affect and disturb the gut microbiota and negatively impact on digestive health. A high-quality diet may therefore help to regulate the gut microbiota and reduce stress and inflammation in the brain and subsequently maintain proper cognitive function throughout life (Haghighatdoost et al., 2019; Tolkien et al., 2018; Wang et al., 2018a). Interestingly, recent data reinforced the potential of microbiota-mediated amelioration of age-related neuroinflammatory pathologies and cognitive decline, and demonstrated that a supplement of prebiotics attenuates age-related microglia activation (Boehme et al., 2019). Likewise, the detrimental behavioral, cognitive and neurochemical effects of stressed adolescent rats were normalized by diets enriched in omega-3 polyunsaturated fatty acids, eicosapentaenoic acid, docosahexaenoic acid, and docosapentaenoic acid and vitamin A and also lead to shifts in microbiota composition (Provensi et al., 2019).

While gut microbiota composition is determined by the host's genetics, and external factors, such lifestyle, the key determinants of gut microbiota composition and function remain, namely diet and nutrition (David et al., 2014; Portune et al., 2016; Turnbaugh et al., 2009; Xu and Knight, 2015). Indeed, dietary factors have been shown to directly shape the microbiota in both rodents (Daniel et al., 2014; de Wit et al., 2012; Marques et al., 2015; Mujico et al., 2013; Murphy et al., 2010; Patterson et al., 2014; Ravussin et al., 2012) and humans (De Filippo et al., 2010; Turnbaugh et al., 2009; Xu and Knight, 2015), and diet therefore represents a modifiable determinant of gut microbiota composition. For example, studies have already shown that high fiber diets and Mediterranean diets, promote a diverse gut microbiota, and are associated with a reduced likelihood of depression (Gopinath et al., 2016). In addition, fermented foods may also have potential to modify the gut microbiota and to alter gut physiology and mental health (Aslam et al., 2018). Thus, it is clear that gut microbiota has potential to impact on mental health, but the mechanisms by which this comes about has yet to be elucidated (Scriven et al., 2018). Mechanistic studies aimed at the identification of the molecular mechanisms underpinning the effects of the gut microbiota on centrally regulated processes are urgently needed. Future studies should identify diets that can modulate brain functioning through specific bacterial strains producing centrally active metabolites.

9. Towards a better science-based advice on nutrition

Epidemiological studies have demonstrated that diet has an impact on mental health and intervention studies support this relationship. In addition, individuals with defined genetic and non-genetic disorders such as in lactose intolerance, phenylketonuria and gluten sensitivity profit from ad-

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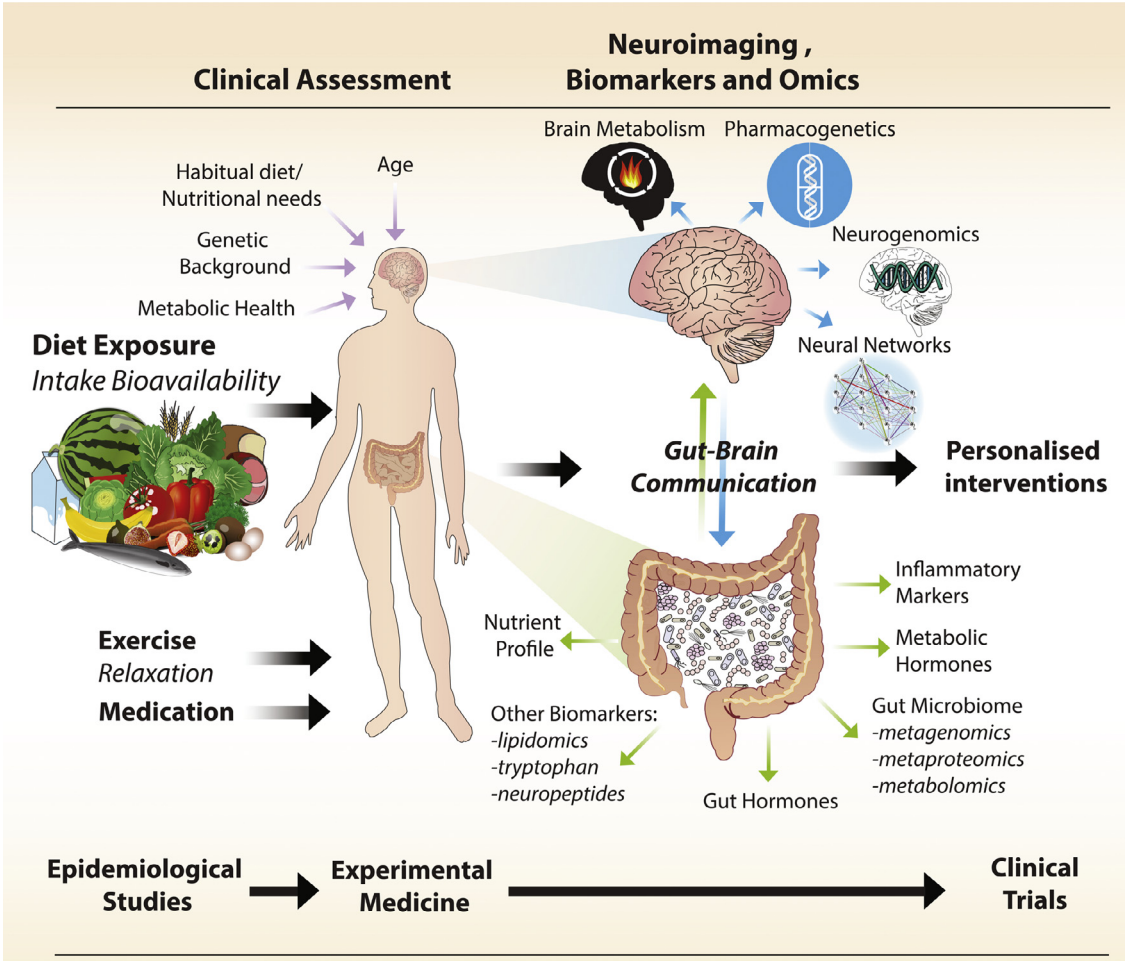

Fig. 1 Integrated nutritional intervention and care in affective disorder studies and treatment.

hering to particular diets. Still, many associations are disputed; strong evidence for a causal mechanism is exceedingly difficult to obtain. We know little about the specific dietary components that provide a benefit for mental health for the individual. This research gap needs to be addressed if a solid evidence base for dietary advice in relation to mental health is to be developed. Several hurdles need to be overcome. To be able to utilize diets for mental health, a mechanistic understanding is required regarding (1) how diet affects metabolic processes in gut (including microbiota), (2) how this impacts on signaling from gut to brain (including via gut hormones), (3) how diet affects levels of metabolites in blood and target organs, (4) how cells and cellular networks (neural networks) respond, (5) how genetic background impacts on the influence of diet on mental health, and (6) how diet impacts on gene expression and downstream effects. Elucidating the metabolic and cellular mechanisms and pathways through which nutrition can promote the resistance of neurons to insults and improve mental fitness will help us to determine how best to modulate diet composition in order to promote mental health throughout life.

The challenge for "Nutritional psychiatry" is to develop comprehensive, cohesive and scientifically rigorous evidence-based research that defines the role of diet and nutrients in diverse aspects of mental health (Jacka et al., 2017; Marx et al., 2017; Sarris et al., 2015a, 2015b). Specifically, the link between the body exposure to specific micro- and macronutrients (that depend on intake, bioavailability and metabolic function and organ systems involved) and a wide array of mental health issues (that include, for example, mood, cognitive processes and stress resilience) and that involve direct and indirect mechanisms that modulate neuronal function and synaptic plasticity needs to be better defined.

Much effort has been expended in establishing large cohorts for nutritional research. Now is the time to data mine and utilize the information gathered from such cohorts to define novel mechanistic hypotheses that can be tested using experimental medicine approaches (Fig. 1). Experimental medicine studies provide a bridge between preclinical investigations of mechanisms and clinical trials. Importantly, they employ experimental design in a laboratory setting to ensure rigor and clear endpoints (Dawson et al., 2011). Individual eating styles and dietary habits should also be taken into account as they influence overall dietary intake and diet quality independently of depression (Paans et al., 2019). Therefore, the use of high

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quality and adequately powered experimental population studies will provide new mechanistic insights into the relationship between nutrition and mental health. It will then be possible to identify interventions that have a higher probability of succeeding when tested in larger RCTs.

10. New concepts

Nutritional interventions are different from pharmacological interventions. drugs act via one or a limited number of targets for which the drugs have a high affinity, which usually is below the submicromolar range. Probably because their affinity is in the same range, vitamins are the only known nutrients that can be studied in a manner similar to drugs. Most nutrients are consumed in much larger amounts than drugs, and their affinity for proteins is much lower than for drugs. Since levels of nutrients and their metabolites reach much higher concentrations, they bind and affect a variety of targets. Thus, in general, nutrients and their metabolites act upon multiple targets in multiple organs. While many studies have examined the effects of individual nutritional components or foods on brain and behavior, nutritional research is shifting from a focus on single nutrients or supplements to dietary pattern analysis (Hu, 2002). This is important because nutrients may act together to affect specific functions and interactions between specific nutrients may affect their bioavailability thus complicating the identification of specific substrates. In the case of nutraceuticals that are not found in foods, such as N-acetyl-L-cysteïne and S-adenosylmethionine, the picture is further complicated by the emerging evidence that some combinations of compounds have synergistic effects, whereas other combinations have been found to be ineffective (for a recent review of nutraceuticals and a related view on nutritional psychiatry see Sarris, 2019).

Most dietary interventions do not include a placebo as control condition, since the design of a control product is a challenge for trial design. Arguably, it may be easier to show the impact of specific nutrient deficiency than that of adding a nutrient or food in a controlled situation. Evidence on the effects of supplementation with nutraceuticals is mixed and does not provide strong support for their use in psychiatric disorders (Sarris, 2019). Essential nutrients are required for normal physiological function but cannot be synthesized in the body and thus must be obtained from the diet. A poor diet may lack sufficient amounts of essential nutrients, but do we know all essential nutrients? Perhaps too low amounts of a given nutrient or the combination of lower levels of specific nutrients increases the susceptibility for cognitive decline. Moreover, there may be individual differences in the sensitivity and requirement of essential nutrients. Indeed, genome wide association studies (GWAS) and meta-analyses have identified strong effects on levels of blood and urine metabolites. Identifying such nutrients in an individual may be challenging, but is required to improve personalized dietary advice. A recent study revealed an association between the genes in the regulation of blood/urine metabolite levels and mental disorders (Hebebrand et al., 2018). Further research is warranted to extend these initial links beyond the DNA-level. As such, the identified metabolites should be measured in both diseased and healthy individuals to verify the relationships. Potentially RCTs can then be set up to determine if specific dietary interventions can alter the serum concentrations of metabolites that differ systematically between patients and controls. As such, a new concept emerges: genetic data are used to identify potential targets for dietary interventions aimed at altering the serum level(s) of one or more metabolites in patients with specific mental disorders (Fig. 1).

11. Conclusion

Accumulating evidence provides support for the existence of direct relationships between nutrition, stress susceptibility, mental health and mental function throughout the lifespan. However, the evidence is correlational and there is a gap in understanding how these effects come about. Novel breakthrough findings on the bidirectional relationships between nutrition and brain functioning are urgently needed to inform public health policy on diet. Improved mechanistic understanding of how nutrition affects mental health and cognition will guide the development of new nutritional interventions and evidence-based advice that will promote and maintain brain fitness throughout life. The promotion of dietary habits that lead to better mental health, and the identification and validation of critical individual nutritional components, will improve sustainability in our healthcare systems and reduce the economic costs associated with poor mental health and cognitive decline.

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None.

Contributors

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Declaration of Competing Interest

Eline van der Beek has a position at Danone.

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