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EDITORIAL

Editorial focused issue 'The role of nutrition in child and adolescent onset mental disorders'

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Childhood neurodevelopmental and psychiatric disorders are known to be complex conditions of multifactorial aetiology, involving both genetic and environmental determinants. There is a rapidly growing awareness that mental symptoms and psychiatric disorders are linked to nutrition. This focused issue of *European Child+Adolescent Psychiatry* will present a state-of-the-art overview of the topic of nutrition and child and adolescent psychiatric disorders, with the aim of moving this highly promising field forward by formulating a research agenda and to inform clinicians regarding the currently available therapeutic and preventive options.

Food intake affects brain development and function in all age groups, starting from the phase in utero in terms of cognitive processes, mood, and brain performance. Accordingly, nutritional deficiencies can result in a vast array of age-dependent clinical symptoms, which affect the function of the central nervous system. Nutritional insults can have a particularly strong effect on the developing brain between weeks 24 and 42 of gestation, during which several neurologic processes, including synapse formation and myelination build upon one another [1]. A remarkable plasticity is a core feature of the young brain, thus potentially allowing for substantial repair after appropriate nutrient repletion. However, vulnerability to nutritional insults seemingly outweighs the plasticity of the brain at this early age; structural and/or functional damage may persist after repletion [1]. The central effect of nutrient deficiency or supplementation is dependent on the requirement of the central nervous system for a nutrient in specific metabolic pathways and structural components. A specific nutrient may promote normal brain development at one time point and be toxic at another. Furthermore, different concentrations of nutrients may be required during development. Concentrations of several nutrients are tightly regulated (e.g., iron) with aberrant brain development ensuing from both a deficiency and an excess. Important nutrients during late fetal and early neonatal life include protein, zinc, iron, copper, choline, and polyunsaturated fatty acids (PUFA; 1).

Prenatal exposure to an 'unhealthy diet' has been associated with ADHD symptoms, further linked to altered epigenetic modification of blood-derived DNA [2]. The study by Daraki et al. in this issue [3] illustrates how low maternal serum vitamin D concentrations during the first trimester were related to behavioral difficulties, especially ADHD-like symptoms, at preschool age in the child. As vitamin D amounts of the developing fetus are dependent on maternal stores, maternal vitamin D deficiency is of great concern for its consequences in the offspring. Maternal vitamin D performs a number of biological functions that are fundamental to early brain development [4], including proliferation and differentiation of brain cells [5], regulation of axonal growth [6], calcium signaling within the brain, and neurotrophic and neuroprotective actions [6]. These results may suggest that appropriate supplementation of vitamin D during pregnancy may reduce the incidence of behavioral difficulties and ADHD-like symptoms later in life in the offspring.

The systematic review by Föcker et al. in this issue [7] illustrates that based on the results from 25 cross-sectional studies and 8 longitudinal studies, vitamin D seems to play a

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role in the pathogenesis of mental disorders postnatally, too. Findings from supplementation trials further seem to support this hypothesis, although randomized controlled trials in childhood and adolescents are urgently needed to support the potential of vitamin D as a complementary therapeutic option in mental disorders.

Over the last 15 years, considerable interest has also been given to the potential role of PUFA deficiencies for pathogenic understanding of child and adolescent onset mental disorders and, subsequently, to the possible role of PUFAs as adjuvants to pharmacological treatment. Epidemiological and cross-sectional studies have linked aggression/violent behavior with low seafood consumption or low blood omega-3 PUFA levels [8, 9]. A recent meta-analysis concluded that omega-3 polyunsaturated fatty acid (PUFA) supplementation was associated with a small but reliable reduction of ADHD symptoms [10]. Certainly, one of the most spectacular findings came from a placebo-controlled RCT conducted in 231 prison inmates; it showed that supplementation with PUFAs (omega-3 and 6), vitamins, and minerals or placebo led to a 26.3% reduction in disciplinary offences [11]. Grey matter volume of the anterior cingulate cortex may mediate the relationship between omega-3 PUFAs and executive functions linked to cognitive control and impulsivity, demonstrating that the beneficial effects of nutrition on cognitive performance can be observed at the level of brain structure [13]. The systematic review by Tesei et al. in this issue [13] contributes to this area of research by showing that insufficient levels of PUFAs may be related to non-externalizing symptom domains in psychiatry, such as depression, juvenile bipolar disorder, intellectual disabilities, and learning difficulties.

Promising results have also been obtained for elimination diets, which, in the context of psychiatry, aim to identify foods, nutrients, or food additives underlying or contributing to mental symptoms/disorders [14]. However, as described by Ly et al. in this issue [16], it remains inconclusive whether elimination diets are effective as a clinical treatment for children with ASD and ADHD, since the long-term effects (and hence, feasibility in daily life) have not been studied. Furthermore, although several studies using most proximal assessment demonstrated large effects of elimination diets in children with ADHD [16, 17], an overall small effect of this diet was shown by other studies using probably blinded assessments [14].

The main candidate mechanism underlying the elimination diet (and other diets) influencing ADHD and related symptoms is the microbiome–gut–brain axis, involving complex interactions between multiple systems, including the metabolic, immune, endocrine, and neural systems. Animal studies over the last decade have impressively shown that gut bacteria can influence brain chemistry and neural development, affecting among others the physiological stress system, cognition, and different aspects of behavior [18]. On the other hand, the brain can also affect the gut bacteria, such that stress experienced by an organism, for example, can modify the gut microbiome, allowing colonization by pathogenic bacteria, which, in turn, can affect brain functioning [19]. As clearly described by Cenit et al. in this issue [20], evidence from preliminary human studies suggests that dietary components that modulate gut microbiota may also influence ADHD development or symptoms, although further studies are warranted to confirm this hypothesis. Of interest is the fact that gut microbiota undergoes a dynamic non-random process of maturation until the age of 2–3 years when an adult-like microbiota structure is established. Although, later in life, the microbiota may still experience changes, the symbiotic link between the host and the microbiota is thought to be mainly established early in life and occurs in parallel with neurodevelopment. Understanding the early interaction between the intestinal microbiota, the environment, and the host would open new avenues for nutritional/therapeutic interventions in at-risk populations for neurodevelopmental disorders. Nevertheless, as underlined by Herpertz-Dahlmann et al. in this issue [21], major changes in diet later in life, like starvation in patients with anorexia nervosa (AN), have a substantial impact on the gut microbiome. Malnutrition and long-term dieting have a substantial and reproducible effect on the gut microbiome and its impact on the brain [22]. There is growing evidence that the gut microbiome also plays an important role in the persistence of eating disorders, especially AN. Understanding the link between dietary patterns and the microbiome–gut–brain axis in the onset and course of child and adolescent onset mental disorders is a key area of research of the next decade.

It is obvious that mental health and the onset and course of psychiatric disorders cannot be understood in isolation from nutrition. A plea to further integrate psychiatric and somatic research and clinical practice was made by Muskens et al. in this issue [23]. In their systematic review, it was shown that medical disorders in children and adolescents with ADHD and/or ASD appear to be widespread, including immunological, neurological, and gastroenterological disorders. Vice versa, children with medical disorders are at increased risk for developmental disorders, which are unfortunately not often recognized. The authors advice that those who work with children with ASD and/or ADHD should be well aware of this and actively promote routine medical assessment. They further pose a critical view on current health care systems, which are often marked by clear divisions between medical disciplines. Cross-trait linkage disequilibrium score regression revealed genetic correlations between BMI/obesity as in indirect nutritional marker and mental

quantitative phenotypes and categorically defined mental disorders [24], thus further alerting physicians to look beyond the disorder that an individual patient presents with.

Therapeutic efforts to influence brain function via nutrition may appear out of the scope of the daily clinical work of most child and adolescent health care professionals. The multitude of available nutritional recommendations for both children and adolescents to enhance cognitive function and to improve mood can be daunting and confusing. Our knowledge of nutrition and its role in mental processes is scant. The establishment of adherence of a child and his/her family to a particular psychotherapeutic and/or drug regimen is complicated enough; the difficulties inherent to adherence to medium and longer term dietary interventions—particularly if such interventions go beyond the provision of a supplement—may appear insurmountable. Nevertheless, for the sake of our young patients and in light of suboptimal effect sizes for many of our treatments, we should be open-minded with respect to nutritional interventions. Both the costs and the duration of a single (randomized controlled) trial should induce clinical researchers to carefully choose a promising supplement/diet to test in our patients. Obviously, the chance of coming up with a positive result is additionally bolstered by a priori research to select the appropriate disorder/phenotype, to devise a solid design, to maximize feasibility, and to choose the optimal age range of the subjects to be included in a clinical trial.

We need to be aware of the potentially large variation of inter-individual responses to specific nutrients and diets. For example, the postprandial glycemic response (PPGR) was initially thought to reflect the intrinsic property of the consumed food. However, it turned out that a high between subject variability characterizes the response to the same food. In a seminal study, Zeevi et al. [25] devised and validated a machine-learning algorithm that integrated blood parameters, dietary habits, anthropometrics, physical activity, and gut microbiota to accurately predict PPGR to real-life meals. 'One size fits all' dietary recommendations are not consistent with this novel insight into the inter-individual variation; research is warranted to increase our prediction to determine who will benefit from what intervention and to develop stratified/personalized dietary recommendations.

The main conclusion that we draw based on the articles in this special issue devoted to the role of nutrition in relation to child and adolescent onset mental disorders is that nutrition plays a key role in understanding mental health and mental disorders. Addressing this relationship in research and clinical practice is key to moving the field of child and adolescent psychiatry further the upcoming decade.

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