Chapter 4

Integrative Approach to Child and Adolescent Mental Health

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Abstract

The prevalence of mental disorders between children and adolescents is 10–20% worldwide. Research has shown that most mental disorders begin at childhood and adolescence. Neurodevelopmental disorders are classified by which the development of the central nervous system is disturbed and are associated with varying degrees of consequences in one's mental, emotional, physical, and economic states. Recently, research in mental health, neurobiology, and early childhood development supported the case for early intervention and prevention. The causes of mental disorders in children and adolescents are not currently known, but research suggests that a combination of factors that include heredity, biology, psychological trauma, spiritual well-being, and environmental stress might be involved. There are many factors that play into child and adolescent mental health and disorders; therefore, individualized, personalized, and integrative approaches are necessary in therapeutic interventions and prevention. Thus, by ensuring that the needed mental health care competencies are made available in each primary health care team and by assuring fully integrated mental health and other types of health care, primary health care teams would best provide early, efficient, effective, and optimal recovery-based care.

Keywords: child and adolescent mental health, neurodevelopmental disorder, integrative mental health

1. Introduction: growth and development of the brain

The nervous system is derived from the ectoderm—the outermost tissue layer—of the embryo. The neuroectoderm appears in the third week of fetal development and forms the neural plate that is the source of the majority of neurons and glial cells in the mature human [1]. This is called the neural tube which later gives rise to the brain, the spinal cord, and the telencephalon,

which eventually encompasses the two lateral ventricles, which in turn develops into the areas of the brain known as the basal ganglia and the limbic system [2]. Over time, cells cease division and begin to differentiate into neurons and glial cells, creating the main cellular components of the brain. The newly created neurons migrate to various parts of the brain to differentiate into the different brain structures. The fetal brain develops from neurons moving outward from early precursor cells [3]. After the neurons migrate, they grow extensive dendrites (a neuron's input) and axons (a neuron's output), components that allow communication with other neurons via synapses. Synaptic "discussions" lead to the establishment of functional neural circuits that mediate sensory and motor processing, as well as underlying behavior. This establishment is crucial, as the human brain develops the most in the first 20 years of one's life, and development is driven mostly by genetics and environmental factors (GxE hypothesis). At birth, the infant has many more neurons and synapses than it will use as an adult [4]. The strong bond and attachment of infants to their parents are crucial at a young age since their physical and social environments aid to strengthen the neurons that are used repeatedly. As the infant continues to develop, those neurons that keep up active "discussions" develop to perform better and efficiently. Several clinical and animal studies have shown that providing a child in developmental stages an enriched physical or social environment can significantly improve learning and memory, encourage exploration, and decrease fearful responses to new and unfamiliar experiences [5–10]. It can also reduce the impact of genetic or environmental risk matters. Despite these experimental and clinical researches, it is hard to know the relationship between the particular mechanisms of brain development and mental activities. Psyche is a function of the brain, and psychic phenomena and disorders may have neurobiological correlation. According to a longitudinal study, children as young as 18 months may suffer from mental illness as older children do. Risk factors and predictors of mental illness could be identified in the first 10 months of life, and the association of risks found in studies of older children seems to operate already from birth [11]. Even though there is plenty of research, it would be necessary to have further evidence between mental illness and risk factors of children at a young age.

2. Causes of neurodevelopmental disorders

Ten to twenty percent of children and adolescents experience mental disorders worldwide [12]. Research has shown that most mental disorders begin at childhood and adolescence [13, 14]. Neurodevelopmental disorders are classified by which the development of the central nervous system is disturbed and are associated with varying degrees of consequences in one's mental, emotional, physical, and economic states. Developmental brain dysfunction, which can manifest as neuropsychiatric problems or impaired motor function, learning, language, or non-verbal communication are also characterized by abnormal behavioral or cognitive phenotypes originating either *in utero* or during early postnatal life. The causes of mental disorders in children and adolescents are not currently known, but research suggests that a combination of factors that include heredity, biology, psychological trauma, and environmental stress might be involved [15].

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A large cohort study of neurodevelopmental disorders showed a direct association of the severity of the physical condition with most classes of mental disorders. It also showed a strong overlap between physical and mental conditions and their impact on the severity of functional impairment in youth [16]. Specific patterns of comorbidity have important implications for the etiology. Prospective tracking of cross-disorder morbidity will be important to establishing more effective mechanisms for the prevention and intervention of mental disorders [16]. Genomic technology has shown great advances in gathering evidence that the current paradigm of psychiatric research needs to be updated. These studies provided converging evidence across a number of different levels, supporting the hypothesis that genetic risk factors are shared between disorders and challenging the validity of the classification systems currently used in research and clinical practice [17]. Through genomic technology, the growing list of genes that contribute to early onset developmental disorders is in its hundreds. That increasing number is further complicated by the observation that each patient can carry a unique combination of alleles of varying degree of effect that occurs *de novo* or inherited [18]. In the last 10 years, tremendous progress has been made in our comprehension of early onset developmental disorders [19–26]. To date, five main pathways have been identified as candidates for early onset neurodevelopmental disorders: chromatin remodeling, cytoskeleton dynamics, mRNA translation, metabolism, and synapse formation and function [17]. Understanding the symptoms and course of action for each individual, as well as the biology ranging from genetic and environmental risk factors to the neural circuits involved, remains a substantial challenge for geneticists and neurobiologists [27–29]. Many mechanisms of human brain development remain hidden, but neuroscientists are beginning to uncover some of these complex steps through extensive studies [30–32]. Research finds that neurons migrate from their birthplace near the ventricular walls to their final destination in the brain. As they collect together, they form each of the various brain structures and acquire specific ways of transmitting nerve messages. The result is the creation of a precise and elaborate adult network of 100 billion neurons capable of directing a movement in the body, a perception, an emotion, or other brain functions. Both genetic factors and activity-dependent factors play a role in developing the brain's architecture and circuitry.

3. Shifting paradigm in child and adolescent health

In 2000, scientific and clinical research groups were formed to create an agenda for the fifth major revision of the *Diagnostic and Statistical Manual of Mental Disorders* (*DSM-5)* [33]. These groups generated hundreds of white papers, monographs, and journal articles that provided the psychiatric field with a summary of the state of the science relevant to psychiatric diagnosis and faults within the current research in order to fortify knowledge in those fields. In 2005, the *DSM-5* Task Force was commissioned by the American Psychiatric Association (APA) to start revisions from the 1994 published *DSM-4*. The Task Force was also aided by 13 different work groups tasked with focusing on various disorder areas. Despite the great advances in neuroscience and genetic research during the last 20 years, there are still too few reliable genetic or other biomarkers that can reliably guide

the diagnosis of psychiatric disorders. The diagnostic criteria in the *DSM-5* is a concept of neurodevelopmental disorders, such as intellectual disability, communication disorders, autism spectrum disorders, attention-deficit/hyperactivity disorder, specific learning disorders, and motor disorders. As a diagnostic tool, the *DSM* considers different disorders as distinct entities. However, from the diagnostic perspective, such disorders do not classify neatly within their boundaries as the DSM would want it. As an alternative tool for diagnosis and research into psychiatric disorders, the U.S. National Institute of Mental Health (NIMH) introduced the Research Domain Criteria (RDoC) project. This new project strives to create an experimental classification system that can provide a first step toward precision medicine for mental disorders [34]. The RDoC stems from the Research Diagnostic Criteria (RDC), created in the 1970s in response to the problems in diagnosis that the field of psychiatry experienced as it emerged from the shadow psychological domination [35]. In the RDoC, five main "domains"—Negative Valence Systems, Positive Valence Systems, Cognitive Systems, Systems for Social Processes, Arousal/Regulatory Systems—reflect a brain system in which functioning is impaired, to different degrees, in difference psychiatric conditions [36, 37].

The RDoC framework strives to free researchers and investigators from the rigid classification system of the DSM and pursue research questions in psychopathology that take advantage of burgeoning knowledge of complex behaviors and how these relate to specific aspects of brain activity [38]. It provides a set of guidelines for evaluating the strength of hypotheses relating clinical symptoms or impairments to dimensions of behavioral functioning and neural systems. The future of the RDoC is undetermined but will depend on how well the diagnostic system can direct clinicians to concise and effective treatment or prevention strategies for each individual patient [38]. The RDoC approach to clinical research of child and adolescent psychopathology contributes to the understanding of development as an aspect of the heterogeneity within DSM disorders and commonalities across seemingly disparate disorders. Incorporating the RDoC as a diagnostic tool in this area of clinical research promises to be fruitful avenue of research into the root causes and manifestations of mental illness, eventually leading to more precise and patient-specific treatments [39].

4. Early life programming as target for prevention of child and adolescent

Behavioral and emotional mental disorders with a high prevalence frequently commence in childhood or adolescence. With some respect, the fetal origins of adult disease models explain the associations between undernutrition of the fetus and an increased risk of cardiovascular disease, diabetes, and metabolic syndrome in later life [40]. This model has been expanded to include events beginning prior to conception as well as early postnatal life [41]. Three main classes of prenatal exposure were investigated in the late 1990s for a range of general health outcomes: lifestyle factors, maternal mental health, which covers antenatal stress, anxiety, and depression, and teratogenic and neurotoxic exposures to specific toxins found in substance abuse, environmental toxins, and prescription medication [42]. Recent human epidemiological

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and animal studies indicate that stressful experiences *in utero* or during early life may increase the risk of neurological and psychiatric disorders, arguably via altered epigenetic regulation. Altered epigenetic regulation may potentially influence fetal endocrine programming and brain development across several generations, resulting in the added attention paid to possible transgenerational effects of stress. Based on existing evidence, it would be possible that prenatal stress, as an epigenetic factor, may become one of the most powerful influences on mental health in later life [43]. Epidemiological studies suggested that gestational exposures to environmental factors such as stress are strongly associated with an increased incidence of neurodevelopmental disorders, including attention-deficit hyperactivity disorder (ADHD), schizophrenia, autism spectrum disorders (ASD), and depression [44–47]. There is growing evidence from human studies showing that early exposures to lifestyle factors and maternal mental health are predictive of child behavioral, emotional, and learning outcomes. Already a number of successful programs have been developed, such as nurse visitation in the perinatal period [48]. Recent emerging evidence shows that current interventions aiming to prevent postnatal depression in women are beneficial and effective not only for women with depression but also for those suffering from anxiety and high stress disorders [49–51].

Fetal programming refers to the way in which environmental events alter the course of fetal development, resulting in lasting modifications in the structure and function of biological systems. Programming refers to the influence of a specific environmental factor at a specific point in development. There are exposures during pregnancy such as maternal mental health, lifestyle factors, and potential teratogenic and neurotoxic exposures on child outcomes. Outcomes of interest are common child and adolescent mental disorders such as hyperactive, behavioral, and emotional disorders. The preconception and perinatal periods offer opportunities for the prevention of harmful fetal exposures. Therefore, it is imperative that during the perinatal period maternal mental health prevention efforts should be most strongly advocated and developed. Interventions developed with evidence-based advisement for the perinatal period could later be instituted into the public health system and grow toward universal and targeted interventions. In the course of time, such interventions are likely to have lifelong effects on mental and physical health [52].

5. The role of inflammation in child and adolescent mental health

Data from human and laboratory animals provide compelling evidence that stress-relevant neurocircuitry and immunity form an integrated system that evolved to protect organisms from a wide range of environmental threats [53]. In particular, the fetal inflammatory response to intrauterine infection seems to contribute to neonatal brain injury and subsequent neurological disability [54]. The preconception and perinatal periods are important because deleterious fetal exposures can be prevented during those periods. Therefore, future mental health prevention efforts must be focused on the critical period as well as prevention models should be developed focusing on the perinatal period. Interventions based on evidence-based recommendations for the perinatal period may occur as the form of public health, interventions that are universal and more targeted. If successful, such interventions can have enduring, lifelong

effects on (mental) health. Extensive experimental studies are being conducted on the precise mechanisms of how latent or persistent inflammation negatively affects neurochemical and neurobiological abnormalities related to schizophrenia and/or autism. By further clarifying such mechanisms, novel immunomodulatory interventions that help prevent abnormal brain development and long-term mental illness suffered by people with prenatal infectious/inflammatory histories can be established [44].

The quality of the fetal environment can be compromised in several ways. Indirect stresses such as endocrine, metabolic, or immune responses of toxins like nicotine or alcohol produces vascular restrictions, thereby impeding oxygen and nutritional supply to the fetus. Direct transfer of maternal glucocorticoids or other agents across the placenta are the other stresses. These stresses include neuro-immune factors that are now being recognized as playing important roles in the etiology of neurological and neuropsychiatric disorders, including immunological processes that target the developing brain and prenatal mental infection. Recent data have elucidated the mechanisms by which the innate and adaptive immune systems interact with neurotransmitters and neuronal circuits to influence the risk for depression. Responses of stress mediated via activation of the inflammasome to secrete inflammatory cytokines, heightened serotonin metabolism, and reduced neurotransmitter availability together with hypothalamic-pituitary-adrenal axis hyperactivity. If this intricate neuro-immune communication network is dysregulated during pregnancy, the maternal milieu can be modified, which enhances the emergence of depressive symptoms, as well as negative obstetric and neuropsychiatric outcomes [55].

There are multiple pathways through which inflammatory cytokines can lead to reduced synaptic availability of the monoamines, which can be believed to be a fundamental mechanism in the pathophysiology of depression. Brain regions that regulate motor and motivation activity (promoting social avoidance and energy conservation) in addition to arousal, alarm, and anxiety (promoting hypervigilance and protection against attack) are involved in the primary cytokine targets in the CNS. Dopamine is fundamental to motivation and motor activity, and cytokines have been found to decrease the dopamine release in the basal ganglia together with decreased effort-based motivation and reduced activation of reward circuitry in the basal ganglia, specifically the ventral striatum [56–59]. Pathogen infection and food antigen penetration across gastro-intestinal barriers are means by which environmental factors might affect immune-related neurodevelopment [60]. The proteins gluten and casein are hydrolyzed in the GI tract into peptides, some of which have been shown to have opioid-like properties and are referred to as exorphins [61, 62]. The immunomodulatory potential of these exorphins is not well-understood, with observations that among the repertoire of digested peptides, some have pro-inflammatory and others have anti-inflammatory effects [63]. A study suggested that a strictly supervised and restricted elimination diet can improve the symptom scores of children with ADHD [64], but up to now, there is neither evidence for food-associated mental diseases nor recommendation for dietary therapies besides the experimental stage. A longitudinal study proposed an association between allergic disorder in early childhood and the development of ADHD in later life [65]. Polymorphisms in the C-reactive protein (CRP) gene were associate both with increased peripheral blood concentrations of CRP and symptoms of post-traumatic stress disorder, especially increased arousal for individuals exposed to civilian trauma [66].

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Currently, it is discussed whether this association is an epiphenomenon or a consequela of the inner-psychic events. The role of hormonal signals operating in pregnancy or early postnatal interactions that is able to alter the sensitivity of certain target tissues, often via altered expression of hormone receptors, to these same hormones in later development [67]. There is also an increasing recognition of mechanisms of resilience that, ranging from effector T cells producing IL-4 to $T\text{-}_{Reg}$ cells with anti-inflammatory properties, there is a variety of T cell responses and their neuroprotective effects. For the development of new anti-depressant therapies, a better understanding of such neuroprotective pathways and of the inflammatory mechanisms, ranging from inflammasome activation to cell trafficking to the brain, would be important [68].

6. Integrative approaches to improve child and adolescent mental health

Human beings, in health and disease, are complex systems of dynamically interacting biological, psychological, social, energetic, intellectual, and spiritual processes. There are many factors that play into child and adolescent mental health and disorders; therefore, individualized, personalized, and integrative approaches are necessary in therapeutic interventions and prevention. Complex, interrelated causes, and consequences are understood to be parts of adolescent mortality, sexually transmitted disease, pregnancy, substance abuse, and depression. Therefore, categorical programs targeting only single type of problem behavior and seeking simple solutions are not adequate [69]. Prospective follow-up studies on youth have shown that child and adolescent mental disorders are related to a wide array of adverse outcomes [70]. Recent epidemiological studies have shown that about one fourth of youth experience a mental disorder in the previous year, and approximately one third across their lifetimes. For children, anxiety disorders were most frequent, followed by behavior disorders, mood disorders, and substance use disorders in that order. The difference in rates across the world can be explained by both methodologic factors and true cultural differences in childhood disorders and their magnitude [71]. Recently, research in mental health, neurobiology, and early childhood development supported the case for early intervention and prevention. For instance, according to epidemiologic surveys, some mental health disorders had an early age of onset while an association between increased risk of mental health disorders as an adult and early symptoms was found in other studies [72]. Another research emphasized recognizing the importance of early developmental screening and interventions, in addition to issuing related anticipatory guidance for pediatricians [73]. The other research also increased the understanding of how cognitive and emotional developments in older children and adolescents were related. Newly found evidence on age of onset, risk factors, and effective prevention strongly suggest that early identification and intervention in the primary care environment is important. The range of primary care practice includes a wide variety of activities, such as promoting well-being, preventing illness, and diagnosing and treating illness. A practice to meet children's mental health needs must have a similarly wide scope of activities. This comprehensive approach should consider the full scope and intensity of social, emotional, and behavioral problems influencing children and adolescent. Such an approach needs strategies targeted to different levels of need and coordinated between the systems serving children. Three levels

of intervention exist in mental health—namely, prevention and health promotion, early intervention, and treatment, and using validated and standardized tools for screening and assessment used to identify and treat emotional and behavioral problems earlier.

The way people receive health care is being transformed by the technology in new and exciting ways. Electronic and mobile devices for mental health are available for various conditions, but implementation into clinical practice is low [74]. Also, there is no evidence that using novel media is promoting mental health, but new diagnostic entities have been introduced in the DSM-5, such as Internet addiction. Also, service providers can deliver cost-effective and innovative care to geographically distant areas. Still issues have to be solved with regard to data integrity and security [75].

E-mental health care is defined as mental health services through the Internet and related technologies [76]. E-health is a broader concept which has an information and communication technology (ICT) to connect patients and physicians in real time [77]. According to systematic reviews of the computerized treatments of common mental health problems (therapist-assisted and self-directed), E-mental health treatments were shown to be more effective than zero treatment and equally effective as face-to-face treatment [78]. A clinical study has shown that the effect of computerized interventions for children and adolescents with depression and anxiety [79].

E-therapy is an emerging and fast developing field of research and practice that involves the application of digital technologies to assist or deliver psychotherapy. Currently, a vast majority of E-therapy programs have been developed for adults. It is imperative to find a more suitable and user-friendly method to treat children and adolescents. E-therapy programs for children and adolescents need to take in to account developmental considerations. Also, evidence-based research and further discussion would be needed to determine the optimal forms of delivery and efficiency of E-therapies in clinical environment.

Virtual reality (VR) involves a computer-generated simulation of a three-dimensional image or environment. The use of a VR platform offers an effective treatment option for improving social impairments commonly found in autism spectrum disorder [80]. VR appears to be a promising and motivating platform to safely practice and rehearse social skills for children with ASD. New virtual reality games dealing with motor coordination were tested with children having developmental coordination disorder [81]. The findings will offer essential information on whether such electronic games would have a positive impact on the children's physical and mental health [81]. Mental disorders and substantive mental health problems in children and adolescents are complex phenomena with regard to the pathoetiology, social, and clinical expressions and in the interventions that can ameliorate, modify, or prevent onset, effects, or negative outcomes [82]. On the other hand, it needs to be investigated which interventions are effective, separating these from the ones without effect or adverse effects. To meet the mental health care needs of young people and their families, convergence, not isolation, of professional identities is required. This change is affected by advances in scientific knowledge and clinical therapeutics, as well as changes in social forces and importance of convergence. Thus, by ensuring that the needed mental health care competencies are made available in each primary health care team and by assuring fully integrated mental health and other types of health care, primary health care teams would best provide early, efficient, effective, and optimal recovery-based care [83].

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