

The Science of Brain and Biological Development: Implications for Mental Health Research, Practice and Policy

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Abstract

Objective: This article provides a summary of the complex interaction between genetics and experience which shapes the development of neurobiological systems, particularly in the prenatal/early childhood and adolescent periods. **Method:** Key factors that influence brain structure and function, and mechanisms through which experience impacts risk for mental health disorders presented in this Special Issue are linked with suggestions for future directions in child and youth mental health research, policy and practice. **Results:** Suggested areas to apply evidence presented in this Special Issue include: enhancing research in the differential impact of psychoactive drugs on the developing brain; introducing content on brain and biological development to professional development and post-secondary curriculum; increased involvement of the family in recognition, prevention and treatment of mental health disorders; and, creation of evidenced-informed child and youth mental health policies. **Conclusions:** As more evidence accumulates on how early experience impacts the structure and function of the developing brain, these findings should be applied to how mental illness may be better prevented, recognized and treated in child and adolescent populations.

Key words: *brain development, mental health, child, adolescent, policy*

Résumé

Objectifs: Résumer les aspects complexes de l'interaction entre la génétique et l'expérience qui modèle le développement des systèmes neurobiologiques, notamment pendant la période prénatale, la petite enfance et l'adolescence.

Méthodologie: Les principaux facteurs qui influent sur la structure et le fonctionnement du cerveau, les mécanismes par lesquels les expériences vécues ont une incidence sur le risque de maladie mentale – qui sont présentés dans ce numéro spécial – servent à proposer des thèmes de recherche sur la santé mentale de l'enfant et de l'adolescent, sur la politique et sur la pratique clinique en santé mentale. **Résultats:** Les données publiées dans ce numéro spécial pourraient trouver des applications, et être notamment utilisées pour intensifier la recherche sur l'impact différentiel des substances psychoactives sur le développement du cerveau; proposer un cours sur le cerveau et son développement biologique dans les formations professionnelles et dans l'enseignement de premier cycle; accroître la participation de la famille dans la reconnaissance, la prévention et le traitement des troubles de santé mentale; instaurer une politique de santé mentale de l'enfant et de l'adolescent basée sur des données probantes. **Conclusion:** Une meilleure compréhension des expériences vécues dans la petite enfance et de leur influence sur la structure et le fonctionnement du cerveau en développement permettra de mieux prévenir, détecter et soigner les troubles de santé mentale chez les enfants et les adolescents.

Mots clés: *développement cérébral, santé mentale, enfant, adolescent, politique*

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Introduction

As we further our understanding of the development of the brain and its relationship to other biological systems (such as the endocrine and immune systems) in the prenatal/early childhood (substantially prior to age five years) and adolescent (substantially between ages 10-19 years) periods, it is becoming increasingly clear that historic debates about the ascendancy of genetics (nature) or that of the environment (nurture) have been superseded by an as yet evolving understanding of the complex interaction between nature and nurture that shapes the growing child: emotionally, socially and behaviourally. It is through our increasing understanding of this complex interaction between genes and environments and the outcomes of that interaction on other environments encountered by the individual that we hope to advance our ability to understand and promote mental health and better prevent, identify and treat mental disorders, so as to improve outcomes for young people, their families and their communities.

Child and adult mental disorders and their prevalence in Canada

The lifetime prevalence of mental disorders in children and adolescents is estimated at 13-18% of the Canadian population. The most common are: anxiety disorders, attention-deficit hyperactivity disorder (ADHD), conduct disorder, and depressive disorders (Costello, Mustillo, Erkanli, Keeler, & Angold, 2003; Waddell, Offord, Shepherd, Hua, & McEwan, 2002). Half of all lifetime cases of mental disorders have an onset before age 14 and three quarters by age 24. Most of these are the initial manifestations of what will become chronic conditions persisting into adulthood. Patterns of persistence include but are not limited to: onsetting and remitting; persisting within a limited range of severity; and, persisting with waxing and waning ranges of severity (Kessler et al., 2005). The neuropsychiatric disorders contribute substantially to the burden of illness across the life span and as a group constitute the largest such burden in young people (World Health Organization, 2003).

If not effectively addressed, these disorders have pervasive and negative impacts on well-being, daily functioning and increase rates of both short- and long-term morbidity (for example, Weissman et al., 1999). Individuals with mental disorders experience more difficulty maintaining social relationships, less academic and vocational success, a greater risk for substantial physical illnesses (such as diabetes and heart disease) and are at higher risk for early mortality, including a substantially elevated risk for suicide (Gould, Greenberg, Velting, & Shaffer, 2003). These difficulties are translated into broader social problems, with rates of mental disorders in the population of incarcerated youth as high as 70% (Kutcher & McDougall, 2009).

Mental disorders comprise a substantial financial burden on the economy. The economic burden of mental illness in Canada was estimated at over \$50 billion in 2003, including direct medical costs, work loss (comprised of both absenteeism and unemployment), and loss in health-related quality of life (Lim, Jacobs, Ohinmaa, Schopflocher, & Dewa, 2008). Despite the significant burden on society, mental health, and child mental health in particular, is an underserved, underfunded and neglected area of health care (Kirby & Keon, 2006).

Neurodevelopment and gene-environment interactions

Epidemiological evidence reveals an association of experiences in the prenatal and early childhood period with later health and well-being. The brain develops rapidly during this period, a time during which experiences shape the developing brain, with implications for health, learning and behaviour throughout the lifespan (McCain & Mustard, 1999). These environmental influences include: emotional (such as caretaker bonding); social (such as family interactions); and, biological (such as quality and type of nutrition) influences.

Positive early experiences, including a stable and nurturing caregiver, a language-rich environment and access to good quality nutrition, medical care and community supports, provide a strong foundation for lifelong health and well-being. Negative early experiences, including neglect, abuse, poverty or a lack of adequate nutrition and stimulation, are associated with an increased risk of poor long-term outcomes including increased rates of chronic physical diseases, mental disorders and low educational attainment (McCain & Mustard, 1999).

For example, work by Felitti and colleagues reports associations between the number of adverse child experiences (including child maltreatment and household dysfunction) and risk of poor outcomes in adulthood including mental health disorders, poor physical health, and early death (Felitti et al., 1998). Epidemiologic evidence of associations between early experiences and later outcomes is supported by neurodevelopment research revealing the environmentally sensitive nature of the structures and neurobiologic pathways in the developing brain during the prenatal period and early years of life (Anda et al., 2006; Glaser, 2000).

During this period of rapid development, experiences interact with the genetic endowment to drive brain development through various processes, including but not limited to brain plasticity and epigenetics. Brain plasticity refers to the development and strengthening of neural connections in response to environmental stimuli, resulting in the creation

and enhancement of various neural pathways (“cells that fire together, wire together”) and the “growth” of brain regions associated with specific functions (such as larger cortical representation for unique components of motor movement). Epigenetics refers to the regulation of gene expression through mechanisms that do not change the DNA coding (Blumberg, Freeman, & Robinson, 2010). Epigenetic modifications affect how DNA impacts the brain’s cellular machinery through enhancing, depressing, turning on or turning off genes. Gene-environment interactions have been studied in relation to mental health outcomes. For example, Caspi et al. (2003) report the modification of the association between stressful life experiences and depression through polymorphisms of the serotonin transporter gene (5-HTT). Individuals with one or two copies of the short version of the allele had higher rates of depression than those without the short version of the allele. Similar findings involving a polymorphism for monoamine oxidase A (MAOA) were reported in male children exposed to maltreatment. MAOA activity moderated the relationship between exposure to maltreatment and antisocial behaviour later in life (Caspi et al., 2002).

The articles in this issue provide an overview of early brain and biological development and neurobiological mechanisms that influence the development of mental health disorders. They provide insights in how we may be able to construct conceptual, procedural and infrastructural components of our inter-personal, social and institutional networks to support positive outcomes, decrease risk for negative outcomes and potentially delay, or prevent the onset or impact of mental disorders.

Kolb and Gibb (in press) identify a number of environmental factors that influence the developing brain in the pre- and early postnatal periods, with evidence primarily from rat but also human and non-human primate models. The influence of these factors including but not limited to: sensory and motor input; psychoactive drugs; relationships (with peers and caregivers); and, physical/emotional stress are relevant to mental health practitioners. Kolb and Gibb conclude that everyday experiences that may have previously been assumed to be non-significant can have substantial and potentially long-lasting effects on the developing brain. For example, exposure to psychoactive drugs in the prenatal and infant stage has been shown to alter development of the prefrontal cortex and thus, behaviours related to that area in rats. These may also influence later plasticity (Kolb, Gorny, Li, Samaha, & Robinson, 2003). Relationships with parents and peers have a significant influence on both the structural and functional development of the brain. Significant perturbations in the early social environment may lead to emotional/behavioural disturbances in the early years that also negatively impact long-term social functioning (Kolb & Gibb, in press). These findings suggest

that there may be specific environmental stimuli that can either inhibit or enhance brain development that results in both short- and long-term emotional, social, behavioural or cognitive functioning. This should pave the way to further work that can help untangle the complexity amongst various factors involved.

Hassel and colleagues (Hassel, McKinnon, Cusi, & MacQueen, in press) describe the psychological and neurobiological mechanisms through which negative early experiences result in an elevated risk for mood disorders. Neurobiological mechanisms consist of gene-environment interactions, regulation of the HPA axis, and structural brain changes. Psychological risk factors including temperament, cognition, autobiographical memory, facial emotion processing and decision making are areas where literature has demonstrated a link between negative childhood experiences and increased risk for mood disorders. The neural networks and impaired functional processes associated with negative experiences impair social and cognitive functioning leading to maladaptive behaviour, which can further heighten the risk for mood disorders. Interventions targeted at reducing the impairment in functioning could mitigate this cycle by reducing maladaptive behaviours resulting in heightened risk.

Suomi’s (in press) article identifies research findings in non-human primates (primarily rhesus monkeys) that demonstrate gene-environment interaction and maternal buffering through attachment relationships formed primarily through face-to-face interaction between mother and infant. The experience of being reared by mothers and peers early in life compared to that of being reared by peers only has been shown to be protective of infants with versions of alleles that constitute high risk, for example in genes including 5-HTT responsible for serotonergic function and MAOA associated with levels of aggressive behaviour. The early rearing environment (mothers and peers or peers only) has been demonstrated to impact the structure and function of the brain including neuroendocrine reactivity, neurotransmitter metabolism, and gene expression, as well as the behaviour and emotional regulation of rhesus monkeys. Further research on the influence of secure attachment relationships on brain structure and function in humans will inform prevention and intervention initiatives targeted at caregiver-infant interactions.

Implications for prevention and early intervention of psychiatric disorders

The available evidence regarding the impact of early experiences on development and gene-environment interactions has important implications for psychiatric research and practice as well as mental health policy. More study is

needed, including longitudinal research involving large and heterogeneous cohorts to help us better untangle the complex interactions described above. However, our current and much improved understanding of the childhood roots of mental illness, and the contributions of and interactions between genetics and experience may be able to inform prevention of and early intervention in mental health disorders, with the potential to improve both short- and long-term outcomes across a variety of domains.

Future Research Directions

A developmental understanding of mental illness is essential for early identification, prevention and treatment. Research into the genetically clocked timing of development of neurobiological pathways and how environmental inputs interact with them will contribute to this understanding. Localization and networks associated with various functions in the brain and how they change over time, and the change in expression of symptoms throughout development are also key areas of study that are needed to be furthered to inform psychiatric education and practice (Costello, 2010).

Using animal models in preclinical research is a safe and efficient way to demonstrate the effects of many environmental variables including but not limited to: exposure to external factors including psychoactive drugs; sensory stimulation; and, relationships throughout development (Kolb & Gibb, in press). Collaboration between basic, applied and clinical scientists is needed to maximize understanding of how these findings can apply to clinical practice with humans (Andersen & Navalta, 2011).

Many psychoactive medications administered to pregnant woman and children have not been thoroughly tested for safety and long-term effects in this population. Practitioners are faced with the challenge of effectively treating substantive and impairing psychiatric symptoms and disorders while avoiding negative side effects, both in the short and long term. Psychoactive drugs can have a lasting and significant impact on the developing brain, including influencing later plasticity, and the effect of medications on the developing brain differ from the effects on the adult brain, sometimes even in the opposite direction (Andersen & Navalta, 2011). As more evidence on both short- and long-term medication effects in this population becomes available, understanding the risks of treatment will improve. At the same time, it is necessary to understand that early interventions with psychotropic medications may demonstrate heretofore unknown positive neurodevelopmental effects, both in the short- and the long-term. As always, the benefits and the risks of intervention will guide treatments, and the more and better research illuminated information that we have, the better we will be able to evaluate the risk:benefit ratio.

Child and Youth Mental Health Practice

Practitioners require a developmental understanding of mental illness and the impact of experiences and early relationships with caregivers on the developing brain in order to understand possible primary prevention strategies, better recognize early symptoms of mental disorders and offer best evidence-driven and most cost effective treatment. Effective and appropriately contextualized education about neurodevelopment and the interaction of genetics and environment is needed for all health and human service providers, including those working in health care, education, community services (such as those providing childcare and parenting supports for example), and in the education and justice system. Ongoing best evidence-driven professional education and post-secondary training in these domains can be expected to result in improvements in practice and patient outcomes.

Better involvement of the family in prevention and identification of mental disorders or substantive mental health symptoms in young children could greatly improve our ability to identify, diagnose and effectively treat mental illness in young children. Parents and immediate family members are closest to children, and with appropriate awareness and understanding may be able to detect early symptoms of mental illness. A family history of mental illness is common in those diagnosed and may be an appropriate area for targeted prevention efforts. Mental illness affects the whole family, therefore, prevention and intervention that includes the family unit is an important area for future research (Kutcher, 2010).

Child and Youth Mental Health Policy

In Canada, there are currently no national mental health policies or frameworks for children and youth and it is the minority of provinces and territories that have created such policies, including British Columbia, Alberta, Saskatchewan and Ontario (Kutcher, Hampton, & Wilson, 2010). Those that are available do not meet the World Health Organization (2005) suggested criteria for comprehensiveness. Mental health policies that define a vision for health, establish a blueprint for prevention and treatment of mental disorders, address recovery of those living with mental disorders and promote mental health in the community are necessary to guide the development and application of research and its most appropriate application (World Health Organization, 2001). They should be based on best available evidence that must come from best available scientific research. It is the translation and application of this evidence that is a challenge not yet effectively undertaken. For example, although much is yet to be learned, enough is already known (as evidenced in the papers of this issue) to inform better and more comprehensive and cost effective

health and social policy. In one sense, it is not that we do not know what could be done, it is that we are not doing it.

Evergreen, the recently completed national child and youth mental health framework for Canada, was developed under the direction of the Child and Youth Advisory Committee of the Mental Health Commission of Canada. The creation of Evergreen included broad collaboration between youth, parents, educators and mental health professionals through an innovative online creation and public consultation procedure (Kutcher & McLuckie, 2011). Evergreen consists of six values underpinning strategic directions in promotion, prevention, intervention/care and research/evaluation. The framework can be accessed online at www.mental-healthcommission.ca. It is hoped this initiative will be able to help mobilize and better focus child and youth mental health policy development and its effective application by responsible governments and other organizations/institutions Canada-wide.

Conclusion

As more evidence accumulates on how early experience impacts the structure and function of the developing brain, these findings should be applied to how mental illness may be better prevented, recognized and treated in child and adolescent populations. Priority areas to apply this evidence are described in the Implications section, including: enhancing research in priority areas (e.g. the differential effects of psychoactive drugs on the developing brain); introducing content on brain and biological development in post-secondary and professional development courses for students and professionals working with families and children in many capacities; involvement of the family in prevention, intervention and treatment of mental health disorders; and, development and implementation of evidence-informed child and youth mental health policies. Policies that support “brain-informed” practice as well as accessible prevention and treatment services will help psychiatrists and other mental health professionals improve long-term outcomes for individuals at risk for mental illness.

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Glossary

Adrenalin – A hormone, secreted when under stress by the medulla of the adrenal gland, that stimulates the heart, increases blood sugar, muscular strength, and endurance, etc.; also called epinephrine.

Alleles – One of two or more forms of the DNA sequence of a particular gene; each gene can have different alleles. Sometimes, different DNA sequences (alleles) can result in different traits, such as colour. Sometimes, different DNA sequences (alleles) will have the same result in the expression of a gene.

Allostasis – The ability to achieve stability through change, a process critical to survival.

Allostatic Load – Through allostasis, the autonomic nervous system, the hypothalamic-pituitary-adrenal (HPA) axis, and the cardiovascular, metabolic, and immune systems protect the body by responding to internal and external stress. Stress promotes adaptation, but prolonged stress leads over time to wear and tear on the body.

Amygdala – A part of the brain that performs primary roles in the formation and storage of memories associated with emotional events. The amygdala is also involved in the modulation of memory consolidation.

Autonomic Nervous System – A part of the peripheral nervous system that acts as a control system for visceral body functions. It affects heart rate, digestion, respiration rate, salivation, perspiration, diameter of the pupils, urination, and sexual arousal. Whereas most of its actions are involuntary, some, such as breathing, work in tandem with the conscious mind.

Brain Architecture – All of the physical structures and components of the brain and how they are created together as a working functioning system. The basic architecture of the brain is constructed through an ongoing process that begins before birth, peaks in childhood and adolescence, and continues into all phases of adulthood.

Brain Plasticity – Behaviours emerge in development as the brain structures and functions underlying specific capacities mature over time. This development represents more than a simple unfolding of a genetic blueprint. It is actually a complex combination of genes interacting with the environment.

Biological Sensitivity to Stress – Individuals vary in their biological sensitivity to contextual risk factors and life events. Children with heightened biological sensitivity to context are both more vulnerable to toxic stress in negative contexts and more sensitive to positive environmental influences when they are in good contexts.

Child Maltreatment – There are five major kinds of child maltreatment: physical abuse, sexual abuse, emotional or psychological abuse,

neglect and intimate partner or domestic violence by adults witnessed by children.

Cortisol – A steroid hormone produced by the adrenal cortex that regulates carbohydrate metabolism and maintains blood pressure. Also called hydrocortisone.

Depression – A complex disorder that can be manifested through a variety of emotional, physical, and other associated symptoms (e.g., anxiety, worry, and pain).

DNA Methylation – A type of epigenetic change involving chemical modification of DNA that is stable over rounds of cell division but does not involve changes in the underlying DNA sequence of the organism. Epigenetic change is an important aspect of cellular differentiation, allowing cells to stably maintain different characteristics despite containing the same genetic material.

Dopamine – A monoamine neurotransmitter formed in the brain and essential to the normal functioning of the central nervous system. Dopamine is the main neurotransmitter of the reward system and becomes dysregulated in addiction.

Emotion Dysregulation – Often people with posttraumatic stress disorder (PTSD) related to early life trauma – such as child maltreatment – have problems regulating their emotions. The person displays an emotional response that is poorly regulated and does not fall within the normal range of emotive response. Under-modulation refers to symptoms such as reliving flashbacks, vivid memories, and fear or anger states associated with past adverse events. Over-modulation is also common for those who have PTSD. This includes symptoms of dissociation (such as out-of-body experiences), emotional numbing symptoms (being detached from one's emotions), and the inability to feel pain.

Epigenetics – A gene is basically like any other molecule in the cell and thus it is subject to physical modifications. These modifications alter the structure and chemical properties of the DNA, and thus the expression of the gene. Collectively, these modifications can be considered as an additional layer of information that is contained within the genome. This information is thus epigenetic in nature. The name derives from the Greek *epi* meaning “upon” and *genetics*.

Gene x Environment Interaction – A model that emphasizes the complex manner in which genes and environment shape physiology and behaviour through Gene x Environment interactions. For example, genes that shape maternal stress response could impact the environment by influencing parenting behaviour, which, in turn, influences maternal-child interactions. This Gene x Environment effect could subsequently impact child stress response, which, in turn, may influence child behaviour.

Hippocampus – Part of the brain related to the formation and long-term storage of associative and episodic memories. One of several limbic structures that have been implicated in mood disorders. Included in the

functions of hippocampal circuitry are control of learning and memory and regulation of the hypothalamic-pituitary-adrenal (HPA) axis, both of which are altered in depression.

Hypothalamic-Pituitary-Adrenal (HPA) Axis – A major part of the neuroendocrine system that controls reactions to stress and regulates many body processes, including digestion, the immune system, mood and emotions, libido, and energy storage and expenditure. The HPA axis consists of a complex set of direct hormonal influences and feedback interactions between the hypothalamus (part of the brain, located near the brain stem), the pituitary gland (a pea-shaped structure located below the hypothalamus), and the adrenal glands (small conical organs on top of the kidneys). The HPA axis activates and terminates the release of stress hormones in response to stress.

Maternal Buffering – Positive effect of having a nurturing caregiver relationship, an important protective factor that fosters better health and appears to overcome some genetic risk for poor outcomes.

Myelin – An electrically insulating biomolecule that helps speed the conduction of electrical impulses in nervous system cells. Myelin is essential for the proper functioning of the nervous system.

Neocortex – A part of the mammalian brain that makes up the outer layers of the cerebral hemispheres. The neocortex is divided into frontal, parietal, occipital, and temporal lobes, which perform different functions. In humans, the frontal lobe contains areas devoted to language, decision-making, and social and emotional processing.

Neurotransmitter – A biochemical substance such as dopamine or serotonin that transmits or inhibits nerve impulses at a synapse.

Neurulation – The formation of the embryonic neural plate and its transformation into the neural tube.

Nucleus Accumbens – A part of the brain thought to play an important role in reward, pleasure, and addiction. It may be involved in the regulation of emotions, perhaps consequent to its role in mediating dopamine release.

Prefrontal Cortex – A part of the forebrain that is divided into the lateral, orbitofrontal, and medial prefrontal areas and is involved in executive functions such as working memory, decision-making, planning, and judgment.

Secure Attachment – When infants form strong, positive, and trusting emotional attachments to their mothers and other caregivers.

Serotonin – An amine neurotransmitter formed in the brain and essential to the normal functioning of the central nervous system. Serotonin is important in the regulation of mood and arousal.

Social Protective Factors – A positive and supporting person in the life of a child is a major contributor to the overall wellness of the child and can be a significant protective factor. Other people from extended family, school, and other places are also important to positive social development for children and adolescents.

Stress Response – A fight-or-flight response activates the autonomic nervous system, which initiates, within seconds, an integrated, short-onset repertoire of biobehavioral changes associated with accelerations of heart and respiratory rates, sweat production, and other physiological changes.

Synapse – The minute space between a nerve cell and another nerve cell, a muscle cell, etc., through which nerve impulses are transmitted from one to the other.

Thalamus – A part of the brain that relays all information received from the senses (except smell) to the various processing centres in the cerebral cortex. The thalamus regulates the electrical rhythms that parts of the brain use to communicate with each other.

Toxic Stress – Experiences that are severe, uncontrollable, or unpredictable produce an intense physiological response in the brain and body (see Stress Response in this glossary). When these experiences are frequent or long-lasting, this response becomes damaging to biological tissues, including brain matter. For children, being brought up by a mother who is seriously depressed or addicted, being maltreated as a child, or living in a chaotic and unpredictable home situation are toxic-stress experiences. Toxic stress in the early years of life damages the developing brain and can lead to lifelong problems in learning and behaviour, and increased risk for physical and mental illness.

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