Canadian Academy of Health Sciences
Académie canadienne des sciences de la santé

RSC
The Royal Society of Canada
The Academies of Arts, Humanities and Sciences of Canada

SRC
La Société royale du Canada
Les Académies des arts, des lettres et des sciences du Canada

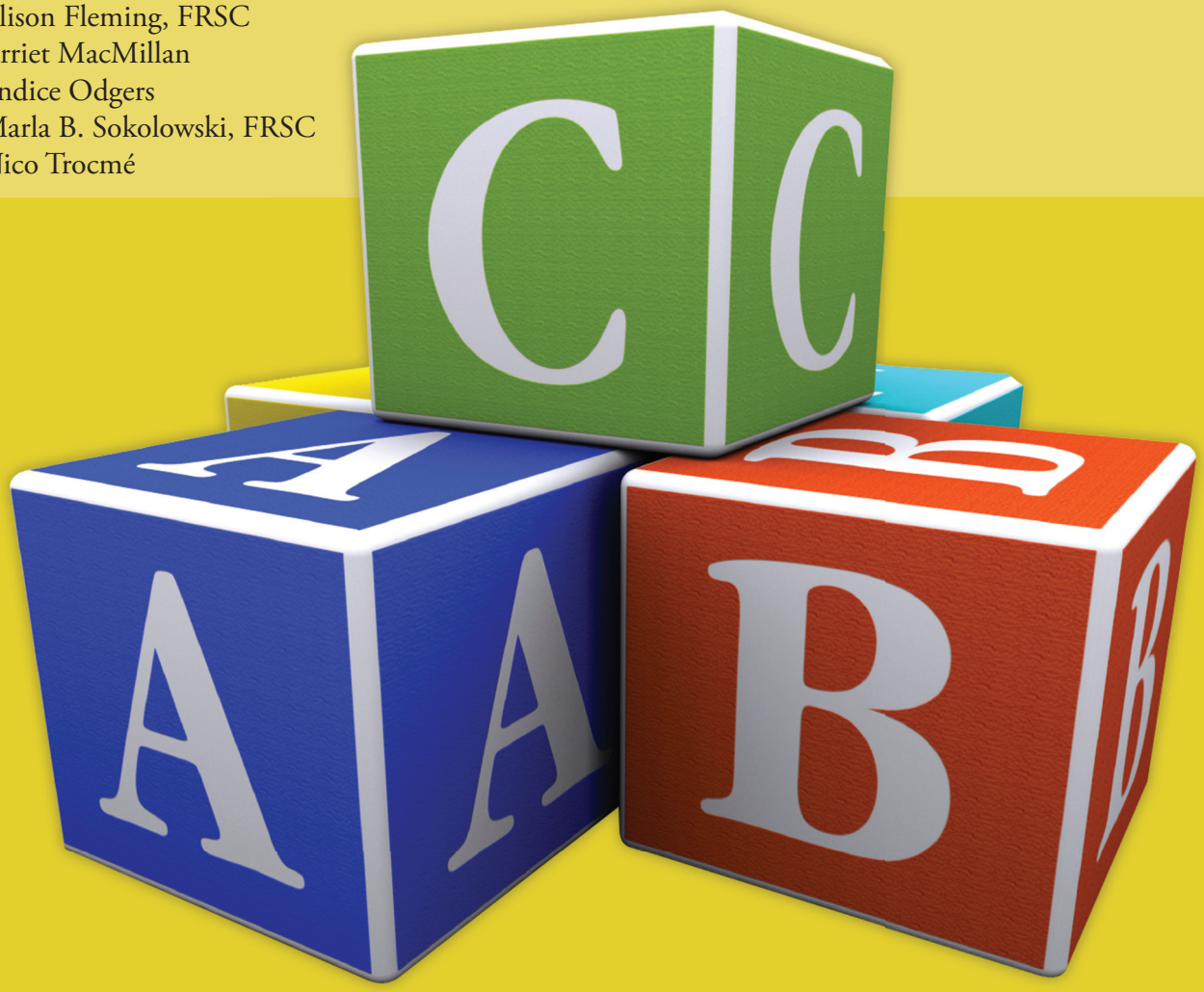
REPORT

The Royal Society of Canada & The Canadian Academy of Health Sciences Expert Panel

Early Childhood Development

November 2012

Prof. Michel Boivin, FRSC (Chair & Editor)
Dr. Clyde Hertzman, FRSC (Chair & Editor)
Dr. Ronald G. Barr
Dr. W. Thomas Boyce
Prof. Alison Fleming, FRSC
Dr. Harriet MacMillan
Dr. Candice Odgers
Prof. Marla B. Sokolowski, FRSC
Prof. Nico Trocmé



Royal Society of Canada/Canadian Academy of Health Sciences Expert Panel (RSC/CAHS)

EARLY CHILDHOOD DEVELOPMENT

Co-Chairs and Editors:
Michel Boivin
Clyde Hertzman

Panel:
Ronald G. Barr
Michel Boivin
W. Thomas Boyce
Alison Fleming
Clyde Hertzman
Harriet MacMillan
Candice Odgers
Marla B. Sokolowski
Nico Trocmé

Research Associate:
Constance Milbrath

Production Assistant:
Agata Stefanowicz

Information Specialist:
Michele Wiens

The Royal Society of Canada and the Canadian Academy of Health Sciences acknowledge and are grateful for the financial support of the Norlien Foundation.

Date: November 15, 2012

The report should be cited as follows:

Boivin, Michel, & Hertzman, Clyde. (Eds.). (2012). Early Childhood Development: adverse experiences and developmental health. Royal Society of Canada - Canadian Academy of Health Sciences Expert Panel (with Ronald Barr, Thomas Boyce, Alison Fleming, Harriet MacMillan, Candice Odgers, Marla Sokolowski, & Nico Trocmé). Ottawa, ON: Royal Society of Canada Available from: https://rsc-src.ca/sites/default/files/pdf/ECD%20Report_0.pdf

Table of Contents

EXECUTIVE SUMMARY — EARLY CHILDHOOD DEVELOPMENT

Early childhood is an extremely sensitive period in human development, during which the brain, especially the circuitry governing emotion, attention, self-control and stress, is shaped by the interplay of the child's genes and experiences. As children grow, the biological and environmental factors that determine their development become increasingly intertwined. When the environment is a secure, positive one, these factors join forces to help maximize their potential. But when children face enduring obstacles to healthy development, such as poverty, inappropriate care, or violence, environment and biology may route them on a course to emotional, physical and mental health problems.

To advance public discussion on the role of early adversity in shaping adolescence and young adulthood, the Royal Society of Canada and the Canadian Academy of Health Sciences asked an Expert Panel on Early Childhood Development to produce a consensus document on these questions:

1. Are there identifiable adverse childhood experiences such as abuse, neglect, chronic poverty, family dysfunction, chronic illness, family addiction and/or mental illness that lead to poor mental health and unhealthy behaviours, such as addiction, in the adolescent and young adult? Is there evidence that they have their effects through changes to brain structure and function? Do these factors operate together to produce their changes? Are there factors that mitigate the influence of adverse early experiences?

2. What is the evidence for the effectiveness of a variety of interventions to mitigate the adverse effects of environmental influences [including social, political and chemical/biological] on the developing child? To what extent are such interventions being implemented in Canada?

It is now clear from extended longitudinal research that children who, early in life, face chronic adversities such as family poverty, inappropriate care, and child maltreatment are more likely to

experience a broad range of impairments later in life. These difficulties range from emotional, behavioral, interpersonal, school and stress-related adjustment problems, to more severe difficulties such as mental health problems, delinquency and criminal offending. Needless to say, these difficulties may have dire consequences for the individual and society.

Early adversity and later developmental health are linked through the structural and functional development of specific brain and nervous system circuits, most notably the stress-response system. These brain development processes are partly governed by complex gene-environment interactions affecting the expression of genes. By gene-environment interaction, we mean that (multiple) genes convey a general susceptibility that may result in a negative outcome depending upon the child's experience of environmental stressors. Our genes do not determine our traits; rather there is a dynamic interplay between nature (genes) and nurture (environment). Developmental trajectories appear early in life and then tend to be reinforced subsequently through a cascade of differential exposures to stressful and risky social contexts.

This report outlines an emerging science, which integrates genetics, epigenetics, neuroscience and developmental science, and that will transform our knowledge of early development by providing a deeper understanding of how the environment and biology jointly influence development over the life course. Here are some of the issues raised by this new science:

Genes listen to the environment, and their expression is partly influenced by experience. Recent advances in epigenetics, mainly using animal models, now provide us with mechanisms that explain how this may happen biologically. There is emerging evidence in humans suggesting that brain development could be partly molded through changes in gene expression, embedding early experience in our biology and leading to individual differences in developmental health trajectories. More research is necessary to tell to what extent this is the case.

Exposure to early adversity is a significant predictor of later problems, but not inevitably in all children. Rather, children vary tremendously in their response to adverse childhood experiences; there is no single path from early adversity to poor social, emotional, cognitive, and mental health outcomes. The effects of early adversity are moderated by a wide range of factors, from genes to community-level social support.

Early childhood is a sensitive period when children may be more susceptible to both negative and positive exposures. Some children may be more biologically susceptible to social context than others, and thus more predisposed to react to both stressful and nurturing environments. These children could also experience the most gains from intervention.

Adverse childhood experiences are not just about dramatic events; day-to-day interactions in children's lives are more important than we previously understood. It is the chronic exposure to maltreatment, poor parenting and other adversity rather than an individual occurrence of maltreatment that is most damaging to developmental health.

The biological systems and pathways linking adverse childhood experiences to biology and behavior also extend to the regulation of parenting behaviors. We need to invest in services aimed at enhancing and supporting sensitive and effective parenting in various contexts. Such support should be ongoing and complemented through childcare, school and community programs aimed at laying the foundations of better health and preventing addictions and mental health problems. Beyond parenting, broader factors—at the level of the extended family (e.g., grandparents, aunts), community and society—also play an important developmental role. We need to understand how and to what extent these factors affect child development.

There is now a limited but promising body of research showing that child maltreatment, perhaps the most serious adversity that children may encounter, and its associated outcomes can be reduced if targeted, intensive and sustained services are deployed. In contrast, there is a paucity of credible research evidence on how broader interventions at the level of the community might influence adverse childhood experiences in ways that, in turn, would influence long-term developmental outcomes. While poverty is a key risk factor for child maltreatment, it is rarely addressed in child maltreatment intervention programs.

The success of intense, sustained prevention programs targeting high-risk families around birth and early childhood underlines that time as a high-priority window for intervention.

SOMMAIRE EXÉCUTIF — LE DÉVELOPPEMENT DES JEUNES ENFANTS

La petite enfance est une période névralgique du développement humain pendant laquelle le cerveau, et plus particulièrement l'ensemble des circuits régissant les émotions, l'attention, la maîtrise de soi et le stress, se développe en fonction de l'influence mutuelle des gènes et des expériences de l'enfant. Pendant la croissance du jeune enfant, les facteurs biologiques et environnementaux qui déterminent son développement s'imbriquent progressivement. Lorsque l'environnement est rassurant et favorable, ces facteurs se conjuguent pour maximiser son potentiel, mais lorsque le développement du jeune enfant est constamment menacé par des obstacles tels que la pauvreté, des soins inadéquats ou de la violence, de tels environnements et sa biologie peuvent se liguer contre lui et le conduire à des problèmes d'ordre émotionnel, physique ou mental.

Afin d'alimenter la discussion publique concernant l'influence de l'adversité en bas âge sur la vie des adolescents et des jeunes adultes, la Société royale du Canada et l'Académie canadienne des sciences de la santé ont demandé à un groupe d'experts sur le développement des jeunes enfants de produire un document consensuel qui répond aux questions suivantes :

1. Existe-t-il des expériences défavorables, telles que la maltraitance, la négligence, la pauvreté chronique, une dysfonction familiale, une maladie chronique, une dépendance à une substance ou une maladie mentale chez un membre de la famille, qui conduisent à des troubles de santé mentale ou de comportement, tels qu'une dépendance, chez l'adolescent et le jeune adulte? Avons-nous des preuves que ces expériences agissent en modifiant la structure ou le fonctionnement du cerveau? Ces facteurs se combinent-ils pour produire ces changements? D'autres facteurs peuvent-ils atténuer l'influence de l'adversité sur les jeunes enfants?

2. Quelles données probantes démontrent l'efficacité des diverses interventions déployées pour atténuer les effets défavorables des facteurs environnementaux [d'ordre social, politique ou chimique/biologique] sur le développement de l'enfant? Dans quelle mesure ce type d'intervention est-il pratiqué au Canada?

Il est maintenant clair, d'après de nombreuses études longitudinales, que les enfants exposés en bas âge et de manière chronique à des formes d'adversité comme la pauvreté familiale, des

pratiques parentales inadéquates et la maltraitance, risquent davantage d'éprouver des difficultés ultérieures au cours de leur vie. Ces difficultés couvrent des problèmes émotionnels, comportementaux, interpersonnels, scolaires ou de gestion du stress, tout autant que des difficultés plus importantes, telles que troubles mentaux, délinquance ou criminalité. Il va sans dire que ces difficultés peuvent avoir de graves conséquences pour la personne concernée et pour la société.

Le lien entre l'adversité en bas âge et la santé développementale ultérieure s'explique par le développement structurel et fonctionnel de certains circuits du cerveau et du système nerveux, plus particulièrement le système de réponse au stress. Ces processus de développement du cerveau sont en partie régis par des interactions gènes-environnement complexes qui influencent l'expression des gènes. Par *interactions gènes-environnement*, on entend que les gènes (multiples) transmettent une susceptibilité générale qui peut se traduire par des conséquences négatives si l'enfant est exposé à des stresseurs environnementaux. Nos gènes ne déterminent pas notre personnalité; il s'établit plutôt une relation d'interdépendance dynamique entre l'inné (les gènes) et l'acquis (l'environnement). Les trajectoires développementales émergent en bas âge et se renforcent subséquemment par une suite d'expositions différentes à des situations stressantes et risquées.

Ce rapport fait état d'une science en émergence qui, s'appuyant sur la génétique, l'épigénétique, les neurosciences et la psychologie du développement, transformera notre connaissance du développement de la petite enfance en nous aidant à mieux comprendre comment l'environnement et la biologie interagissent pour influencer le développement humain. Voici certaines questions soulevées par cette nouvelle science:

Les gènes sont à l'écoute du milieu et s'expriment partiellement en fonction des expériences vécues. Des percées dans le domaine de l'épigénétique, principalement basées sur des modèles animaux, révèlent maintenant des mécanismes qui expliquent comment cela se traduit sur le plan biologique. Les premières études chez l'humain laissent entendre que le développement du cerveau pourrait être en partie modelé par de tels mécanismes. Le cas échéant, les expériences de la petite enfance pourraient conditionner notre biologie et engendrer des différences dans les trajectoires développementales individuelles. D'autres recherches seront nécessaires pour déterminer la mesure de ces effets.

L'exposition précoce à une adversité constitue un précurseur important de problèmes ultérieurs, mais à des degrés divers selon les enfants. En effet, la réponse des enfants aux expériences défavorables varie énormément; il n'existe pas de cheminement unique reliant l'adversité en bas âge à des problèmes sociaux, émotionnels, cognitifs ou mentaux ultérieurs. Les impacts de

l'adversité sur les individus varient selon un large spectre de facteurs allant des gènes au soutien social dans la communauté.

La petite enfance est une période névralgique, puisque les jeunes enfants sont plus sensibles aux expositions négatives et positives. Certains enfants peuvent être plus sensibles que d'autres sur le plan biologique à des contextes sociaux et, par conséquent, plus prédisposés à réagir à des environnements stressants et stimulants. Ces enfants pourraient également tirer les plus grands avantages d'une intervention.

Les expériences défavorables de l'enfance ne concernent pas seulement les événements dramatiques; les interactions quotidiennes dans la vie de l'enfant sont plus importantes que nous l'avions cru. Les effets les plus néfastes sur le développement sont davantage le résultat d'une exposition chronique à de la maltraitance, à un soutien parental inadéquat et à d'autres formes d'adversité qu'à un événement unique de maltraitance.

Les systèmes et les voies biologiques liant les expériences précoces à la biologie et au comportement se rapportent également au développement des comportements parentaux. Nous devons investir dans des services destinés à favoriser la mise en œuvre de pratiques parentales sensibles et efficaces dans divers contextes. De tels services de soutien devraient s'inscrire dans une perspective à long terme et être complétés par des programmes préscolaires, scolaires et communautaires destinés à promouvoir une meilleure santé et à contrer les problèmes de dépendance et de santé mentale. Au-delà du soutien parental, des facteurs plus généraux — à l'échelle de la famille élargie (grands-parents, tantes, etc.), de la collectivité et de la société — sont également plus susceptibles de jouer un rôle développemental important. Nous devons mieux comprendre comment et dans quelle mesure ces facteurs influencent le développement de l'enfant.

Quoique limitée en nombre, des recherches démontrent maintenant que la maltraitance, sans doute la forme d'adversité la plus grave, et ses conséquences peuvent être réduites si des services ciblés, intensifs et soutenus sont déployés. En revanche, nous disposons de peu de données de recherche crédibles sur la façon dont les interventions à l'échelle de la communauté pourraient influer sur les expériences défavorables des jeunes afin qu'elles influencent à leur tour leur développement à long terme. Bien que la pauvreté constitue l'un des principaux facteurs de risque de maltraitance envers les enfants, elle n'est que rarement prise en compte par les programmes de lutte contre la maltraitance envers les enfants.

Les résultats positifs obtenus par les programmes intensifs et soutenus de prévention, qui ciblent les enfants de familles à risque à la naissance et à la petite enfance démontrent que cette période constitue une fenêtre d'intervention prioritaire.

PREFACE

Twenty-three percent of Canadian youth (ages 12 to 19) and 34% of Aboriginal youth, report that their perceived mental health is something less than very good or excellent (Butler-Jones, 2011). It is during adolescence that many mental illnesses, which can persist throughout life, begin to manifest. Abuse of alcohol and recreational drugs have also ruined the health and gravely altered the life course trajectories of adolescents. Health Canada's 2010 Canadian Alcohol and Drug Use Monitoring Survey indicate that alcohol and drug use among adolescents are still serious problems (Health Canada, 2010). Although the report of past year use of marijuana, other illicit drugs [cocaine or crack, speed, ecstasy, hallucinogens or heroin] and alcohol by Canadian youth (15-24 years of age) has decreased since 2004, in 2010 past year use by youth of cannabis (25%) was reported to be 3 times higher than use by adults (25 years and older = 8%) and use of other illicit drugs (7.0%) was reported almost nine times higher than adult use (0.8%) (Health Canada, 2010). The prevalence of past-year drinking among youth (71.5%) was lower than reported by adults (78.0%) but the prevalence of heavy frequent drinking among youth (9%) was approximately three times higher than adult rates (3.3%).

It is now generally accepted that child, adolescent and adult mental health, effective functioning and well-being all result from a complex array of biological, social and environmental factors interacting over the life course. However, the developmental processes through which these different determinants operate need to be clarified. In order to advance public discussion on the issue of the role of early adversity, the Royal Society of Canada and the Canadian Academy of Health Sciences created an Expert Panel on Early Childhood Development. It was convened to produce a consensus document on the following questions, based on a synthesis of the existing peer-reviewed research literature:

1. Are there identifiable adverse childhood experiences (ACE) such as abuse, neglect, chronic poverty, family dysfunction, chronic illness, family addiction and/or mental illness that lead to poor mental health and unhealthy behaviours, such as addiction, in the adolescent and young adult? Is there evidence that they have their effects through changes to brain structure and function? Do these factors operate together to produce their changes? Are there factors that mitigate the influence of adverse early experiences?

2. What is the evidence for the effectiveness of a variety of interventions to mitigate the adverse effects of environmental influences (including social, political and chemical/biological) on the developing child? To what extent are such interventions being implemented in Canada?

The Panel addressed these questions in six parts, highlighting the most recent scientific evidence relevant to each question. The Introduction sets the context; articulating the life course and bio-ecological developmental perspective adopted by the Panel. The second chapter outlines evidence from longitudinal studies dealing with the association between ACE and the risk of poor mental health and unhealthy behaviours in adolescents and young adults. Chapter three presents models of how early adversity might get under the skin to create the vulnerabilities that result in adverse outcomes. Chapter four takes this a step further by delving into the developmental biology of parent-child interaction, especially mother-child interaction, as the

principal pathway that delivers nurturance or adversity to the developing child. In the Introductory and following three chapters, our strategy was for the panelists to draw liberally on the most rigorous research across all relevant fields, in order to create a plausible and up-to-date understanding. Chapter five examines what is known, and what is not known, about interventions to improve mental health and unhealthy behaviour, whose rationale is to reduce childhood exposure to adversity. In this chapter, panelists followed the approach taken by those doing systematic reviews of interventions internationally; focusing on high-quality literature syntheses and studies of interventions with control groups, notably randomized controlled trials (RCTs), focusing on abuse in early life as an exemplar.

These chapters draw our attention away from the broad determinants of child development and initiatives taken in Canada; focusing it, instead, on the family, where the most is known and understood about early adversity, interventions and consequences. Accordingly, the concluding chapter puts our findings back in a broader social and political context. It addresses the problem that contemporary policy and action lag far behind the scientific advances that characterize our understanding of development; and tries to make explicit the relation between what we know about the origins of unhealthy behaviours and mental health, and what we, as a society, should be doing about them.

Finally, it needs to be clearly stated that this report is about adverse experiences *early* in life. The Panel believes that developmental periods are linked together, such that success in one phase of child development can have a significant influence on success or difficulty in later development. We recognize that there are many interventions for unhealthy behaviours and mental health problems that occur during teenage and young adulthood. The focus of this report is on what we know and what we should be doing in earlier stages of development, prior to those stages when behaviour and mental health problems manifest themselves.

CHAPTER ONE: INTRODUCTION AND SETTING THE CONTEXT

Confronted with accelerating social changes in an increasingly global economy, Canada must meet the challenge of nurturing, socializing, and educating the next generation of citizens. This national effort, in turn, needs to rely on a keen understanding of the nature and processes of early childhood development, and a clear appreciation of the role that social environments may have early in life.

Early childhood is characterized by excitement, new experiences and opportunities for positive development. Young children's rapidly developing brains and bodies are primed for input from the social world. Parents are often astonished by the transformations that their children undergo between birth and school entry and science confirms that early childhood is a period of unprecedented change, growth and integration at both the biological and social level. Recent advances in developmental neurobiology also tell us that there is a high level of plasticity in this early phase of brain organization. The malleability and openness to experience that typify early childhood are considered an asset allowing for rapid acquisition of the language, cognitive skills, and emotional competencies required for challenges that lie ahead. Nurturing experiences in the early years may indeed have lifelong benefits, including increased abilities to learn, greater achievement, involvement in community activities, active participation in the labour market and overall quality of life. Early child development, population wellbeing, and societal adaptation are thus tightly linked, and understanding the early pathways towards healthy and unhealthy development is paramount to the further promotion of Canada's human and social capital.

Unfortunately, too many Canadian infants and young children are confronted with enduring obstacles to their healthy development, obstacles such as poverty, inappropriate care, and violence. Further, young children's enhanced sensitivity to their social world also means that they are also highly susceptible to Adverse Childhood Experiences *(ACE).* The terms *early adversity* or *ACE* are used throughout the report to refer to both short-term, dramatic events such as discrete episodes of physical abuse or sexual abuse, as well as the chronic stressors that children encounter as they navigate their daily lives (e.g., harsh parenting, parental depression, parental substance use, and deprivation within the home and community). This breadth of definition is important because, as we discuss throughout this report, it is plausible that chronic exposures may be a greater cause for concern than brief and non-recurring exposures, which might be more easily buffered by off-setting protective influences.

Understanding the effects of early adversity on child development is especially relevant in the Canadian context. In 2008 there were 85,440 substantiated child maltreatment investigations (Trocmé, Fallon, MacLaurin, Sinha et al., 2010) and an estimated 610,000 children and their families living in poverty (Campaign 2000, 2010). Countless other children are growing up within families, schools and neighborhoods where they may be exposed to violence, substance use, and daily stressors. These difficulties encountered by young Canadians not only raise moral issues, but represent violations of Canada's role as a duty barer, under the United Nations Convention on the Rights of the Child, to provide children with the environments and opportunities that will allow their developmental capacities to evolve. They are also of far-reaching societal importance for Canada, as they may not only affect children's development, but they could also have a long-term impact on society though lost opportunities in learning, training

and employment, as well as diminished quality of life (Reynolds, Temple, White, Ou, & Robertson, 2011b).

Each of the outcomes that we consider here places a tremendous burden on the lives of children and their families. For example, the difficulties associated with substance abuse alone are projected to cost the Canadian public close to $40 billion annually (Rey, 1995). In the longer term, they may jeopardize society's capacity to engage citizen's participation, to innovate, and to adjust to ongoing changes and challenges. Parents, educators, policy planners, and those invested in the health and wellbeing of children deserve to know to what extent, and how, exposure to adverse experiences influences children's future development. They also want to know if something can be done to alleviate or mitigate the occurrence and negative impact of these early adverse experiences.

1. Our perspective

The questions posed in this report are not new. For the last half-century, the scientific evidence on the importance of the early years for later healthy development has been mounting. This has led to an acceptance of life course epidemiology as a new paradigm in health research (see below). Various reports and meta-analyses have tried to integrate and synthesize this burgeoning work from a variety of disciplinary perspectives (e.g., Shonkoff & Philips, 2000). Since the turn of the new millennium, however, research in the areas of child development, epidemiology, neuroscience, genetics, epigenetics, and prevention has made formidable progress. It is important to take stock of this recent knowledge as it sheds a new light on the role of early childhood experiences. For instance, ongoing longitudinal studies initiated in the 1980s have reached a point where early childhood adversity factors could be linked prospectively to later outcomes. Many of these studies were upgraded, and new ones were initiated that allowed for a more nuanced appraisal of environmental factors and processes. These innovations allowed more detailed assessments of early child and family factors, including genetic and biological markers.

This wealth of information has generated new insights regarding the nature of the links between ACE and later outcomes. We now better understand how persistent ACE may combine with a cascade of ensuing environmental events and contexts to influence future development. We know that poorer early development, before entry into the formal education system, can lead to poor learning in the school system, as well as enhancing risks to physical and mental health in later life. We now better understand how the brain regulates and controls the neurobiological pathways that affect health (physical and mental), learning, and behaviour. Specifically, we know more about how the brain and the periphery communicate dynamically within a stress response system to serve individual adaptation. Gene-environment interplays have been documented, revealing for example, how the negative impact of some ACE could be conditional on the presence of a genetic risk in the individual. Recent advances in developmental neurobiology point to epigenetic processes whereby environmental conditions may "get under the skin", i.e., provoke changes that become embedded in neurobiological systems. Finally, the last decade has seen prevention research generate an increasing number of interventions aimed at mitigating ACE and their negative impact on the developing child.

The resulting picture is one that is typical of a fast-evolving field of knowledge: highly intricate and multifaceted, at times imprecise, and certainly not definitive. Integrating this knowledge in a meaningful way is not an easy task. To better make sense of this wealth of findings, three basic assumptions have guided our report: (1) the need to adopt a life-long developmental perspective, (2) the usefulness of a bio-ecological population health model to describe the multifaceted nature of the environment, and (3) the need to consider the dynamic interplay between nature and nurture in development. We now expand briefly on these emerging paradigms.

2. The need to adopt a life course developmental perspective

Prior to the 17th century, children were viewed—culturally and functionally—as small adults: more diminutive in stature and lacking in adult sensibilities and cognitions, but essentially indistinguishable from the fully matured versions of their species (Ariès, 1962). Stemming from multiple influences that included Renaissance arts and science, the rise of industrial economies and urbanization, the women's movement, and changing views of human nature, there emerged, in the Victorian and modern eras, a new perspective on childhood as a fundamentally separable and conceptually distinctive period of the human life course. Children became regarded as representatives of a different developmental time, the qualitatively distinctive predecessors of adult populations. An array of societal reforms and realignments emanated from this new view of childhood, which was intended to serve the now discrete and special needs of children and young families. Child labor and welfare laws were written and ratified. Childrearing became a parental practice worthy of societal attention, study and moral guidance. Pediatrics, developmental psychology and developmental biology arose as disciplines that were visibly and empirically distinguishable from their parent sciences. Child abuse and child protection became parts of an international lexicon of prevention. The new conceptual discontinuity between childhood and adulthood thus yielded a rich harvest of societal structures, traditions and laws designed to ensure the wellbeing of children in much of western civilization.

An unintended but inevitable corollary of this novel, differentiated view of the human life course, however, was a predisposition to conceptualize childhood diseases as attributable exclusively to early life risk factors and exposures and the diseases of adults as due only to the risks and exposures attending adult behaviour and lifestyles. There arose a 20th century conceptual isolation of childhood from the pathogenic processes that determine adult morbidities, and by mid-century, an adult lifestyle model of disease deemed the prevalent, chronic morbidities of human populations—coronary heart disease and stroke, diabetes, and cancer—to be determined almost entirely by the health behaviours and lifestyles adopted by 20th century adult populations (Kuh & Ben-Shlomo, 2004). Earlier claims that childhood experiences might somehow alter the health trajectories of adult life were abandoned in favor of modern discontinuities between the events of childhood and adulthood.

Such views of childhood as functionally separable from adult life, however, were not to survive an impending empirical flood of findings linking adult chronic disease to processes and experiences occurring decades before, in the earliest reaches of childhood. Three quarters of the young soldiers killed in the Korean war were found to have evidence of early atherosclerotic changes in coronary and other arteries (Enos, Beyer, & Holmes, 1955), presaging coronary heart disease as the leading cause of premature adult mortality. Newly developed birth cohort studies

began to show that respiratory disease in adulthood was associated with disproportionate rates of respiratory illness in childhood (Colley, Douglas, & Reid, 1973). Prenatal exposures to hormones such as diethylstilbestrol (DES) were discovered to underlie the early development of reproductive cancers in young women (Hatch et al., 1998). Breastfeeding in infancy was found associated with healthier blood lipid profiles and lower levels of glucose and blood pressure in adulthood (Lawlor, Ben-Shlomo, & Leon, 2004), and prenatal processes became linked to the development of schizophrenia (Opler & Susser, 2005) and autism (Colborn, 2004).

Whatever the outcome may be of ongoing debates on the strength, character and mechanisms of such associations, there can be little doubt with respect to their underlying, foundational principle: that the biological and developmental origins of adult disease can often be found among pathogenic processes occurring in the first several years of post-conceptual life (Shonkoff, Boyce, & McEwen, 2009; Shonkoff & Philips, 2000). This is true for physical health, as well as for well-being and mental health; hence the use of developmental health as an umbrella term to refer to the variety of outcomes possibly affected by ACE throughout this report. Indeed, an entirely new field of 'life course epidemiology' has arisen, illuminating the long-term health effects of physical and social exposures during fetal and early postnatal life and investigating how differences in the health effects of material and psychosocial conditions vary by the timing or duration of exposures (Kuh & Ben-Shlomo, 2004). Given the known 'incubation periods' of chronic diseases over many years of time, a life course perspective on the origins of these morbidities is a natural and plausible extension of this view (Davey Smith & Lynch, 2004).

3. The usefulness of a bio-ecological population health model

The bio-ecological view of the environment, as it relates to human development, begins with several observations from the book 'Why Are Some People Healthy and Others Not: The Determinants of Health of Populations' (Evans, Barer, & Marmor, 1994). The first observation is that health, as measured by death or morbidities, follows a social economic gradient in developed countries, such that those at the top of the socioeconomic structures of society live much longer than those in the middle who, in turn, live longer than those at the bottom of the spectrum.[1] However, while a large minority of the population in poor socioeconomic circumstances has poor health and development, a majority still does well as adults. Similarly, in the case of those at the top end of the socioeconomic gradient, a considerable minority still has poor development and major health problems as adults. These observations have led investigators to the question of how individual differences play out in development; more specifically, how the social environment "gets under the skin" to make some people vulnerable to poor conditions, whereas others are more resilient. It is reasoned that the brain is critical for the socioeconomic gradient in health, and that it is brain development in the early years, in particular, that affects health and wellbeing as an adult. In the last ten years, scientists have begun to unravel environmental and personal conditions, as well as mechanisms that explain how early experience can, in fact, "get under the skin". It is this perspective that makes question #1 described above (i.e., concerning the bio-social processes underlying the association between early ACE and developmental health), an

[1] Although social inequalities exist according to many other divisions in society: gender, ethnicity, and immigration status, to name a few, socioeconomic gradients are given special consideration here. This is because it was the characteristics of *gradient patterns*, which contrast with the characteristics of dichotomies (e.g., immigrant/non-immigrant) that lead researchers to the life course bio-developmental perspective articulated here.

urgent one to answer, and lends credibility to the prospects that a developmental approach to intervention (as implied in question #2) might prove effective.

The Final Report of the *WHO Commission on the Social Determinants of Health* supports this perspective. 'Inequalities are killing people on a grand scale' was the conclusion they reached, following a three-year investigation of how the social environment where we are born, live, and age influences health (World Health Organization, 2008). They argued that children are often the most severely affected by inequalities of exposure to social and financial deprivation during critical periods of development, which may compromise their mental and physical health. While Canada faces unprecedented challenges related to the treatment and management of chronic health problems that begin early in life, a new generation of scientists are providing us with answers to how experiences in the social world can get under the skin (Miller, Chen, & Cole, 2009). Converging evidence from neurobiology and epidemiology is illustrating ways through which early exposure to adversity may become biologically embedded (Hertzman & Boyce, 2010), epigenetic and gene expression studies are challenging the idea that our genetic code determines our gene expression, by pointing out how early experiences can 'turn genes on and off' (Meaney, 2010). Teams of researchers are finding ways to move from neurons to neighborhoods in the study of children's health and development (Shonkoff & Philips, 2000).

4. The dynamic interplay between nature and nurture in development

Early child development is an emergent property of multiple levels of influence in the complex social ecosystems where children grow up, live, and learn. Understanding the forms of social causation that take place in this context involves several important, qualifying statements about causal thinking. First, exposures to *social conditions bear complex and sometimes non-linear relations* to outcomes of interest. Human developmental outcomes are nested within complex dynamic systems that involve accumulations of exposures over time, complex interactions among multiple causal factors, and disease occurrence that is often a non-linear function of exposure. Second, social causation is *non-specific*, in the sense that exposures to stressors and rearing in disadvantageous circumstances augment risk for a wide range of adverse outcomes, perhaps by generating a *generalized susceptibility* within multiple causal paths (Cassel, 1976; Syme & Berkman, 1976). More generally in developmental psychopathology, the notions borrowed from system dynamic theory and embryology are that of "equifinality", i.e., the possibility that various developmental pathways lead to the same outcome, and that of "multifinality", i.e., the idea that a given initial risk condition may lead to various outcomes (Cicchetti, Rogosch, & Toth, 1998). Third, social causation is *iterative and recursive,* in the sense of involving repeated, self-amplifying exposures over time. Social adversities often involve self-organizing feedback loops in which one traumatic event follows from others, cascading over time and giving rise to intensely negative and stressful social contexts. For example, marital conflict can presage divorce, which in turn often sequentially leads to residential moves, losses of supportive social relationships, and the onset of depression. Fourth, social causation often involves *mundane, rather than exceptional, exposures*. For example, day-to-day child rearing in environments characterized by impoverished parent-child interactions, even without dramatic, catastrophic events, may be implicated in adverse outcomes over time (Hart & Risley, 1995; Kishiyama, Boyce, Jimenez, Perry, & Knight, 2009). Finally, social causation often responds to the meanings that people place upon their experiences.

Despite the intricate nature of social causation, the determinants of early child development are commonly treated as factors that operate independently of one another or, at most, as factors operating simultaneously in multiple spheres. What is often neglected is the extent to which the level and effect of relevant factors in any one sphere depend upon factors normally thought to belong to other spheres. Bronfenbrenner (Bronfenbrenner, 1979) first addressed this by proposing an ecological approach to determinants that spanned from microsystems to macrosystems. Yet, Bronfenbrenner never drew an explicit model of his own. Accordingly other investigators, over the years, have filled this gap with their own bio-ecological models (Lerner, 1996; Sameroff & Seifer, 1983).

Here, we present a version developed for the *WHO Commission on the Social Determinants of Health* (Siddiqi, Irwin, & Hertzman, 2007), called the Total Environment Assessment Model for Early Child Development (herein, TEAM-ECD model), illustrated in Figure 1.1. It was created through a consensus process of researchers, practitioners, and policy-makers from wealthy and developing countries, as well as First Nations groups such that, unlike most other models, it is applicable globally. As a result it has several features that differ from other models. Like other models, TEAM-ECD emphasizes both the distinct character of determinants and the qualities of interdependence that exist among them. Accordingly, it is organized concentrically from micro to macro, according to levels of geographic aggregation (family to global). Although mostly circles, unlike other models, the 'regional' environment is represented as an ellipse impinging upon the sphere of the nation because, in many parts of the world, regions supply what failed states do not. Cutting across the concentric circles are two 'non-geographic' environments: ECD services and the relational community (that is, the community from which the family gets its identity). This latter, included at the behest of First Nations experts, is essential to making a bio-ecological model credible in multi-cultural, multi-ethnic societies like Canada. Finally, civil society is represented in functional terms; mediating the other determinants in ways that either enhance or undermine children's development.

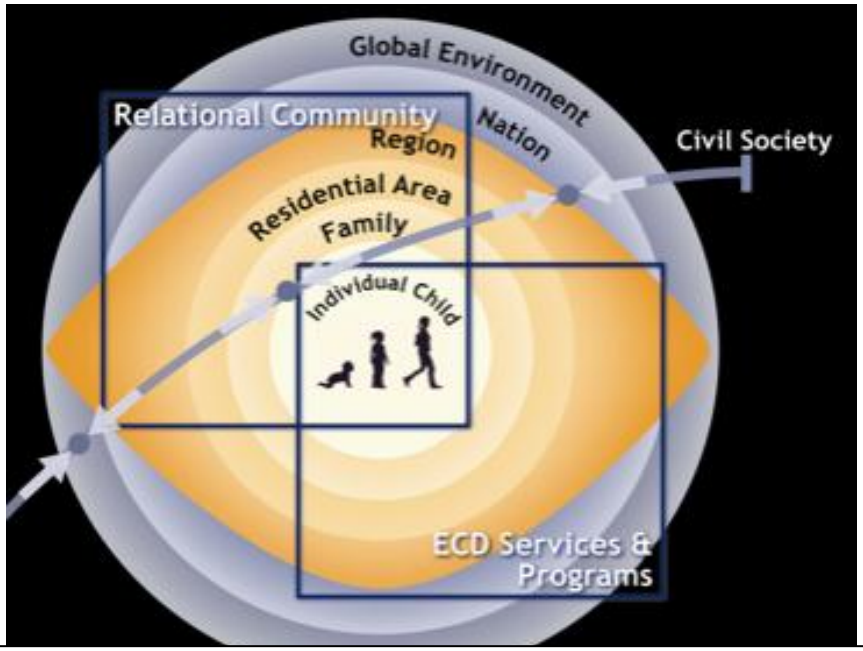


Figure 1.1. *Total Environment Assessment Model for Early Child Development.*

The following paragraphs discuss the role of each determinant in the TEAM-ECD model from the perspective of ACE and their outcomes.

The Individual Child – Disparities emerge early in life in children's physical, social/emotional, and language/cognitive development that are largely attributable to the interplay of genetic factors and systematic differences in the nurturing qualities of their early environments: nutrition, bonding/attachment, stimulation, and opportunities for participation (Boyden & Levison, 2000; Grantham-McGregor, Walker, Chang, & Powell, 1997; Irwin, 2006; Irwin & Johnson, 2005). A dense, hierarchically connected series of sensitive periods occur in brain and biological development during those years, such that early environments can embed themselves in brain circuitry and other biological systems (Hertzman & Boyce, 2010). In recent years it has become clear from animal models that early experiences penetrate to the deepest levels of the biology; changing the way that genes express themselves (Hertzman & Boyce, 2010).

At the same time, mounting evidence shows that the role of early ACE in predicting negative developmental outcomes is not the same for all, but rather depends on children's characteristics, including their genetic make-up (that is, a gene by environment (G x E) interaction). For instance, there is now ample evidence that the environment can affect individuals differently depending on their genetic endowment, and likewise, that the same genetic endowment produces different outcomes depending upon the environment. The complexity of developmental processes is further augmented by the growing flow of negative feedback loops in development, whereby personal characteristics, including genetic factors, may lead to differential exposure to stressful social contexts. In other words, biological and environmental determinants are intertwined in developmental pathways, and new findings concerning gene-environment interplay confirm the complex and conditional nature of social causation described above. The challenge for developmental science now is to better understand how these different processes operate and co-exist in guiding developmental pathways.

Chapters 2, 3, and 4 will speak to these developmental issues more at length, but here we emphasize that the emerging understandings call for the implicit causal beliefs of key actors at all levels of society to be re-examined, so that society can fashion new approaches to policy and action that better manage the complex ecosystem of early human development (Jenkins-Smith & Sabatier, 1994).

The Family – Families provide most early stimuli for children, define the social and economic resources available to the child, and largely control children's contact with the wider environment and the terms upon which it occurs (Richter, 2004; Shonkoff & Philips, 2000; UNICEF, 2007). Social resources include parenting skills and education, cultural practices and approaches, intra-familial relations, and the health status of family members. Economic resources provide material goods (such as healthy foods and adequate dwelling conditions), and help to reduce stress for parents, which in turn supports nurturing relationships between family members, and with children. As one goes from the bottom to the top of families in terms of social and economic resources, child developmental outcomes, on average, improve. This gradient effect, which parallels the mortality gradient described above, is a principal source of modifiable inequality in ECD (Houweling, Caspar, Looman, & Mackenbach, 2005). Gradients mean that the fraction of vulnerable children *gradually* increases, *without a threshold* as one goes from the

most privileged to the least privileged families.

The overall credibility of associations between early adversity and life course morbidity is strengthened by the observation that adversities are not randomly distributed within human populations, but rather are disproportionately present within lower socio-economic status (herein, SES) families and communities (Wadsworth & Santiago, 2008). Beginning early in life, impoverished children and families experience dramatically higher levels of stressors and adversities (Evans & Kim, 2007; Evans & Schamberg, 2009) and sustain higher rates of virtually every form of human malady and developmental hurdles: from low birth weight (Blumenshine, Egerter, Barclay, Cubbin, & Braveman, 2010) to traumatic injury (Brown, 2010), from infectious disease (Dowd, Zajacova, & Aiello, 2009) to psychiatric disorders (Garfield, Zuvekas, Lave, & Donohue, 2011), from developmental disability (Msall, Bier, LaGasse, Tremont, & Lester, 1998) and dental caries (Boyce et al., 2010) to poor academic achievement (Kawachi, Adler, & Dow, 2010). Even among children, SES ranks as one of the most powerful and reliable epidemiologic predictor of human morbidities (Adler et al., 1994; Adler & Newman, 2002; Adler & Rehkopf, 2008; Chen, Matthews, & Boyce, 2002) and developmental problems (Bradley & Corwyn, 2002; Duncan, Brooks-Gunn, & Klebanov, 1994). Although socioeconomic differences in material factors such as nutrition (Khan & Bhutta, 2010), access to medical care (Houweling & Kunst, 2009), and physical environmental exposures (Gump et al., 2007) are important (Hackman, Farah, & Meaney, 2010), the SES-stratified differences in early exposures to family adversities (Wadsworth & Santiago, 2008) also increasingly account for the origins of child health disparities (Brown et al., 2009; Hillis et al., 2004; Kroenke, 2008).

One crucial aspect of this family adversity is parenting. Generally perceived as the cornerstone of early socio-emotional development (Bornstein, 1995), parenting behaviours are especially important in the early years when the maturation of neurophysiological systems makes the infant particularly receptive to, and dependent on sensitive parenting care for his/her emotional and behavioural regulation ((Kochanska, Coy, Tjebkes, & Husarek, 1998); see Chapter 4). Unfortunately, not all children benefit from this nurturing contribution. Early signs of adjustment problems have been associated with inconsistent, non-sensitive, and hostile parenting behaviours ((Lyons-Ruth, Repacholi, & McLeod, 1991; Wakschlag & Hans, 1999); see Chapter 4), although bi-directional and conditional (i.e., interactive) associations with child characteristics are likely ((Boivin et al., 2005; Caspi et al., 2002); see Chapter 2).

Parenting is embedded in a complex social system. It is influenced by parent and child characteristics, but also by contextual stress and supports. As described in Chapter 4, parents bring their personality and personal history to their early interactions with the young child, and this background, as well as more immediate environmental constraints, may influence their beliefs and expectations about parenting, and their parenting practices. Parents' affective state has been associated with the quality of parent-child relations ((Conger et al., 1992; Dix, 1991); see Chapter 4); psychological distress, particularly maternal depression, has been correlated with a reduced ability to pay attention and to process information about the needs of the child, as well as to diminished maternal sensitivity, the use of coercive strategies, physical abuse, and parental dissatisfaction ((McLoyd, 1998); see Chapter 4).

If, in some cases, the reasons for these inappropriate parenting behaviours can be traced back to events earlier in a parent's life (see Chapter 4 for a description of possible developmental processes), there is also a clear association with more contemporary events. A number of studies report a definite connection between actual or recent negative life events and situations and psychological distress manifested in the form of depression, anxiety, hostility, as well as eating and sleep problems (see (McLoyd, 1998) for a review). A restrictive, punitive and emotionally aloof parental style has been associated with stressful and undesirable life events, such as divorce and marital discord (Patterson, Capaldi, & Bank, 1991). SES is of course part of the picture, and has been associated with the psychological well-being of parents and their parental behaviours (Conger et al., 1992). A number of studies show that parents in low SES families are more likely than high SES parents to adopt disciplinary techniques characterized by excessive and restrictive control and more frequent use of disapproval and punishment as a disciplinary method, to attach value to obedience and an absence of support (Hart & Risley, 1995; McLoyd, 1998).

Other studies have shown neurodevelopmental differences across the entire spectrum of SES, not just at the impoverished end, suggesting that role of social position apply to the entire population, albeit to different degrees (Hackman et al., 2010; Hart & Risley, 1995). This has a very important policy corollary: that programs which focus exclusively on low SES or specific risk factors as the criterion for eligibility will miss a large number of children and families who are affected by ACE. In order to reach those most likely to be at risk, there is need for targeted programs, but in order to reach the largest overall proportion of those at risk, there is a simultaneous need for universal programs. This challenge has led to calls for an approach called 'proportionate universality,' that is, programs, services, and policies that are universal, but with a scale and intensity that is proportionate to the level of disadvantage (Marmot Review Team, 2010). This approach will be discussed in the conclusions to this report.

At the same time, low SES children live with significantly more family chaos (Evans, Gonnella, Marcynyszyn, Gentile, & Salpekar, 2005; Repetti, Taylor, & Seeman, 2002), and sustain more frequent and severe psychological stressors (Evans, 2004; Evans & Kim, 2007) relative to their higher SES peers. Thus, in addition to the material exigencies in the lives of lower SES children and families, systematically greater exposures to acute and chronic stress appears to play an important role in the social stratification of child health (Hertzman & Boyce, 2010). Parents psychological distress and their inappropriate parental behaviours might explain the connection between difficult living conditions and later chronic morbidities in the child and in adult life. The degree to which these direct or indirect processes take precedence in the development of negative outcomes is still the object of debate and research, but clearly, families do not operate in isolation. What then are the broader factors that may influence families and their children?

Residential Areas, Relational Communities, and Civil Society – In aggregate, the interconnectedness of individuals within a *residential area* creates a supra-individual, supra-familial, *collective,* social resource. The extent to which individuals are linked to one another; whether there is reciprocated exchange (of information, in-kind services, and other forms of support); whether there is informal social control and mutual support; and whether or not resources are mobilized formally (that is, through programs for children) and informally (that is, treating children like they belong), appear to be key elements. For example, concerns regarding safety for children as well as parents might affect a child's opportunity to participate in physical

activity in venues such as neighborhood playgrounds. Such limitations have a domino effect, inhibiting a child's social experiences. Research shows that the characteristics of residential areas described above may act to diminish the effects brought on by safety issues, as social networks may provide supportive enclaves where families and children feel safe (Sampson, Raudenbush, & Earls, 1997).

In their role as a resource for families with children, these characteristics of residential areas have also been seen as elements of broader constructs: collective efficacy (Sampson et al., 1997), social capital (Coleman, 1988), and the quality of civil society. It is not the purpose of this report to untangle these constructs. Rather, the key point here is that characteristics of the residential environment may play a role children's development in a variety of ways (Beauvais & Jenson, 2003; Drukker, Kaplan, Schneiders, Feron, & van Os, 2006), through stresses (exposure to toxins, and social and psychological conditions such as high crime rates), through the provision of social resources, as described above, through institutions (function of schools, police, neighborhood services, etc.) and through 'epidemic' forces (power of peer influences). There is a considerable literature showing that these characteristics predict children's mental health and learning (Bifulco et al., 2006; Karevold, Røysam, Ystrom, & Mathiesen, 2009; Klein & McCarthy, 2009; Kohen, Brooks-Gunn, Leventhal, & Hertzman, 2002; Levitan, Rector, Sheldon, & Goering, 2003; Nachmias, Gunnar, Mangelsdorf, Parritz, & Buss, 1996; Rao, Hammen, Ortiz, Chen, & Poland, 2008; Repetti et al., 2002; Rikhye et al., 2008). Socioeconomic inequalities among residential communities are associated with inequalities in children's development, but the characteristics described above can buffer or exacerbate socioeconomic factors. Children from low SES families living in economically mixed neighborhoods often do better in their development than low socioeconomic children living in poor neighborhoods (Kohen et al., 2002). Physical spaces accessible to children create both opportunities and constraints for play-based learning and exploration, critical for motor, social/emotional, and cognitive development (Irwin, 2006; James, 1993). Access to high quality services often varies according to community SES: learning and recreation, childcare, medical, transportation, food markets, and opportunities for employment (Leventhal & Brooks-Gunn, 2000).

The *relational* community is the group that gives children and families their primary identity and, often, how outsiders identify them. It is also a source of information regarding child-rearing and parenting norms, especially with respect to harsh parenting. The relational community may be defined by language, religion, ethnicity, geography (*e.g.* rural) or the occupational status of the parents. It is a primary source of prospects for social inclusion or exclusion, sense of self (*e.g.* efficacy, self-worth, self-esteem), and gender norms. The extent to which adults and children in communities are linked to one another, whether there is reciprocated exchange (of information, in-kind services, and other forms of support), and whether there is informal social control and mutual support is, in part, a function of the relational community.

Civil society groups are conceptualized as being organized at, and acting on, all levels of social organization, from local residential through global. The ability of civil society to act on behalf of children is a function of the extent of social capital (Coleman, 1988), and the support of political institutions in promoting expressions of civil organization. When civil society is enabled, there are many avenues through which it can engage on behalf of children. Civil society groups can initiate government, non-government organization, and community action on social determinants

of early child development. They can advocate on behalf of children to assure that governments and international agencies adopt policies that positively benefit children's wellbeing. Finally, civil society groups are instrumental in organizing strategies at the local level to provide families and children with effective delivery of services, to improve the safety, cohesion, and efficacy of residential environments, and to increase the capacity of local and relational communities to better the lives of children.

ECD Programs and Services – When they are of high quality, ECD programs promote competencies and skills for participating in society and the work force (Knudsen, Heckman, Cameron, & Shonkoff, 2006). These competencies and skills are not limited to the cognitive domain, but also include physical, social, and emotional development. Accordingly, ECD programs—which incorporate and link health-promoting measures (e.g., good nutrition, immunization) with nurturance, participation, care, stimulation, and protection—offer the prospect of sustained improvements in physical, social, emotional, language, and cognitive development. More specifically, ECD programs usually address one or more of the following key issues: breast-feeding, developmental monitoring, early childhood care & education, nutrition, parenting, community strengthening, or institutional capacities such as training.

Regional and National – Regions (that is, sub-national political jurisdictions) and nations are important for their capacity to provide, or to deny, families access to societal resources. Although child development tends to be more successful in wealthy than poor countries, the priority given children in social policy can overcome national poverty by enabling families to make positive choices and decisions in the best interests of their children. Kamerman's (Kamerman, Neuman, Waldfogel, & Brooks-Gunn, 2003) review of family policies across countries identified five domains that make a difference: income transfers (cash and tax benefits); employment policies; parental leave and other policies to support maternal employment; early childhood education and care services; and prevention and other interventions related to teen pregnancy. At the regional level, factors that support or undermine family capacity include the physical environment (e.g., transportation, local accessibility of programs and services, family-friendliness of housing market); the degree to which the labour market accommodates families' needs for income and time flexibility; and the policy priority placed upon investments in the early years. Absent these resources, children born into low resource families are more likely to be exposed to conditions that are adverse for development, such as homelessness, crowding, slum living conditions, and unsafe neighborhoods (DiPietro, 2000; Dunn & Hayes, 2000); as well as a variety of forms of parental psychological distress, including negative self-worth and depression (NICHD Early Child Care Research Network, 2002; Patel, DeSouza, & Rodrigues, 2003).

In terms of societal resources to reduce children exposition to ACE and promote healthy development, three features distinguish Canada: a special concern for the First Nations children's experience of ACE, a shared societal and governmental commitment to a social and life course approach to wellbeing and developmental health, and a constitutional framework that while creating variability in the provision of programs across Canada, also sets the stage for regional/provincial innovations, experiments, and comparisons with respect to wellbeing and developmental health. These distinguishing features provide both challenges and opportunities for the future of developmental health in Canada. They are briefly discussed in Textbox 1.1 below.

Textbox 1.1. Canada – Distinguishing features

First Nations children – *First Nations children are significantly overrepresented in Canada's child welfare system. Findings from a 2008 study of a sample of 111 child welfare agencies from across Canada found that First Nations children were 4.2 times more likely to be investigated for maltreatment-related reasons compared to non-First Nations children living in the geographic areas served by sampled agencies, and 12.4 times more likely to be placed in foster care during the investigation. In Manitoba and Saskatchewan, the provinces with the highest proportion of First Nations children, over 80% of children in foster care are First Nations (Sinha et al., 2011). For many observers, these realities are indivisible from Canada's history of placing First Nations children in residential schools; breaking family continuity and undermining parenting and life course traditions. Although residential schools have been closed for decades, their disruptive effects on First Nations families are still felt across generations. Thus, addressing ACE in First Nations populations is difficult to separate from current initiatives being taken to promote reconciliation with the non-First Nations population and to re-build First Nations communities.*

Social and life course approach – *The main governmental agency on public health in Canada, the Public Health Agency of Canada, has embraced a social and life course approach to wellbeing and developmental health. This "Canadian" approach, articulated in the most recent Chief Public Health Officer's report on the state of public health in Canada, is likely to help federate and promote different initiatives across Canada along the lines define in the present report. The following summarizes the approach.*

*It is understood that, in most industrial societies, key life transitions of today are delayed when compared with the life stages of earlier eras. An increase in life course opportunities and less clearly defined boundaries between adolescence and adulthood have altered life stage patterns that identified earlier generations. More time is spent at each life stage; youth complete their education, enter the full-time labour force, leave home, marry or co-habit and bear children later than their parents' or grandparents' generations (*Butler-Jones, 2011*). Canadian society today is also more diverse, with greater inequalities in the education, income, and living conditions of young Canadians (Butler-Jones, 2011). Although more young Canadians are participating in post-secondary education, due to socio-economic, cultural and environmental barriers, First Nations youth are still significantly underrepresented in post-secondary institutions (Kroes, 2008). Such differences subject youth to a variety of stressors and risks that can influence wellbeing and developmental health. Inequalities are best addressed early in the life course in order to maximize the potential of young Canadians to achieve successful life transitions and optimal health (Canadian Institute for Health Information, 2005; Gambone, Klem, & Connell, 2002). The Canadian approach includes efforts to build resilience, reduce stigma, target prevention and intervention for at risk populations as well as promoting health by increasing awareness and education. Addressing problems before they manifest, is of course, the best solution (Butler-Jones, 2011).*

Constitutional arrangements – *In Canada, social services, health and education are the responsibility of the provinces, resulting in high levels of variability in the type, level and cost of service provision across the provinces. Although these circumstances could be seen as a challenge for the application of a uniform and coherent set of policies and programs toward early childhood across Canada, they also provide multiple testing grounds for various policies and services. Each province has actually been experimenting with different arrangements for supporting children and families in the early years. This has lead Canadian researchers to propose pan-Canadian learning indices regarding the strengths and weaknesses of each approach to policy (for example, see (Kershaw & Anderson, 2011; McCain, Mustard, & McCuaig, 2011)). These initiatives should be encouraged, improved, and advocated for in the various constituencies, with the goal of providing a fertile basis for policy innovation and emulation across Canada.*

The Global Environment – The global environment may influence ECD through its associated economic and social conditions within nations. It is also characterized by international treaties, such as the United Nations Convention on the Rights of the Child (UN-CRC), that affirm the rights of children (United Nations & Office of the United Nations High Commission for Human Rights (CRC), 1990) and of the principal care-givers of children, women (CEDAW, 1980). In

particular, General Comment #7, a rider attached to UN-CRC, called 'Implementing Rights in Early Childhood' (United Nations, 2005) creates an opportunity to hold signatory countries responsible for the physical, social/emotional, and language/cognitive development of young children.

TEAM-ECD shows how the factors that influence whether a child is going to end up with adverse outcomes are not merely found at the level of the individual or family, but also at the level of the community and society. Regional, national and global determinants are important because of how they affect families—the proximal factors—not because they operate independently. The insights presented above reinforce the view that the phenomenon of specific environments producing different rates of negative outcomes is not simply a moral issue, but an issue that deals with human biology and, as we show throughout this report, influences that pass from one generation to the next. Notwithstanding this general context, it is important to point out here that the present report does not focus on the macro determinants, but rather largely emphasizes the proximal parent, child and family processes. This is due to the extant body of scientifically credible research that primarily explores the proximal, rather than the distal, determinants of developmental health. This is an important gap that will be discussed in the concluding chapter of this report.

CHAPTER TWO: EARLY ADVERSITY AND THE DEVELOPING CHILD: THE EVIDENCE FROM LONGITUDINAL RESEARCH

Longitudinal studies that have followed large groups of individuals from early childhood to mid-life converge on the message that early experiences can have long-term and cascading impacts on behaviour and health. The aim of this section of the report is to synthesize what has been learned about the contributions of early life experiences to mental health and behaviour problems from cohort studies that have followed children over time, from early childhood into young adulthood. We focus primarily on these longitudinal studies, rather than on studies at one point in time, because, from a methodological standpoint, they provide the 'gold standard' with respect to tracing the long-term outcomes of early adversity.

There are a number of important prospective cohort studies that have informed how early experiences of adversity influence the developing child. Studies such as the *Dunedin Multidisciplinary Health and Development Study (Dunedin Multidisciplinary Health and Development Research Unit), the Montréal Longitudinal and Experimental Study (GRIP Research Unit on Children's Psychosocial Maladjustment), the Québec Longitudinal Study of Kindergarten Children* (*GRIP, Research Unit on Children's Psychosocial Maladjustment),* and the *Christchurch Longitudinal Study (University of Otago)* are featured as they prospectively chart the development of individuals beginning in the early years of life through young adulthood and provide some of the strongest evidence that the effects of experiences during childhood can reach into adulthood. For example, in a recent editorial, John McDermott (McDermott, 2011) heralded the Dunedin Study for drawing a much needed map of the course, causes, and consequences of childhood disorders, and referenced the new generation of longitudinal cohort studies that are positioning themselves to take scientific discovery to the next stage, by integrating state-of-the art assessments of biological markers of early experience (herein, biomarkers) alongside in-depth assessments of familial, school and neighborhood contexts. In this section, we also feature findings from these more recently established cohorts given their potential to fill gaps in knowledge regarding the effects of early experiences on later developmental processes left unaddressed by the previous generation of studies. More recent cohort studies provide added value as they include more frequent assessments during the early years (often starting at or before birth), as well as a host of measures that were not available to prior researchers.

It is important to note that while cohort studies provide evidence that early adversity is *associated* with later life outcomes, longitudinal designs, on their own, are not sufficient to conclusively determine that early experiences are the "cause" of behaviour and mental health problems in adulthood. In addition to the implicit temporal sequence linking the presumed cause and effect, causal inference also requires conditions of control, such as experimental manipulation and random assignment, to be validly assessed. Typically, for ethical or practical reasons, these conditions may only be approximated in research with human subjects. Many of the newer cohort studies have thus attempted to harness 'natural experiments' (e.g., twin and adoption studies) and randomized preventive trials to address some of the common methodological threats to the validity of non-experimental research. However, as will be detailed throughout the chapter, some limitations in making casual inferences from this body of research remain.

An important focus of this section is on the various ways children may be affected by early experiences. For example, not all children who experience maltreatment or harsh parenting develop antisocial tendencies; in fact, the majority of children do not repeat the cycle of violence. Science is now weighing in on the factors that may explain differences between children in their response to the social environment. Consistent with the bio-ecological model of early childhood development presented in the Introduction, we consider how a broad array of determinants, ranging from genetic factors to community-level strengths, may influence children's response to early adversity. We document the broad range of *adverse events* that have been shown to influence children's lives and explore how outcomes may vary based on individual child characteristics (including their genes).

As reviewed below, with the mapping of the human genome completed and the renewed ability to measure genes directly that came with it, the field has shifted towards the measurement of specific genes (candidate genes) that may play a functional role in biosocial models. Genes have now become moving and dynamic targets within social science research, and there are a number of exciting areas of research that are causing us to rethink how environmental factors may interact with genetic vulnerabilities to increase the likelihood of antisocial behaviour. There are good indications that some of these interactions may be time-dependent and non-specific. For example, a series of potentially transformative findings have started to document that children who are carriers of genes that are typically considered 'risky' may also be the ones who experience the most gains from interventions designed to promote positive experiences in early life (e.g., (Bakermans-Kranenburg & van Ijzendoorn, 2011; Bakermans-Kranenburg, Van Ijzendoorn, Mesman, Alink, & Juffer, 2008). These new findings are in line with the notion of a differential biological susceptibility to social context, whereby some children would be more predisposed than others to react to both stressful and nurturing environments (Belsky, 1997; Boyce & Ellis, 2005).

Thus, as the studies reviewed below will illustrate, a 'one-size-fits-all' approach is not sufficient to understand the diverse outcomes among children who experience early adversity. But for the moment, let's start with the recent evidence provided by extended longitudinal observations.

1. Adverse childhood experiences predict poor mental health, behavioural and physical health problems well into young adulthood

Children exposed to adverse experiences, such as maltreatment, harsh parenting, familial psychopathology and poverty are at increased risk for poor outcomes as adults (for a review see Maughan & McCarthy, 1997). During childhood and adolescence, growing up in a family characterized by ACE, including witnessing violence and experiencing various forms of maltreatment, has been linked to high emotional reactivity, lower social competencies, deficits in emotional understanding and the failure to develop effective coping strategies in stressful situations (for a review see (Repetti et al., 2002)).

The idea that adverse experiences during childhood may have negative effects on behaviour and health is not new. However, there has been a renewed focus on the possible long-term and costly effects of ACE due, in part, to findings from the Adverse Childhood Experiences (ACE) Study. The ACE Study is a retrospective study co-sponsored by the Center for Disease Control in the

United States (Centres for Disease Control and Prevention; The Adverse Childhood Experiences Study). Over 17,000 members of a large health management organization in Southern California were surveyed about their history of ACE before the age of 18, including: physical and sexual abuse, emotional neglect, parental divorce and loss, domestic violence as well as exposure to family members with a history of drug and alcohol problems, mental illness and/or crime. There are now a number of widely cited publications from the ACE Study demonstrating strong graded, linear relations between self-reported recall of traumatic or abusive childhood events before the age of 18 and a wide range of mental and physical health problems, including alcoholism, suicide risk, depression, smoking and substance abuse, cardiovascular disease, obesity, chronic lung disease, and cancer (Anda et al., 2006; e.g., Anda et al., 1999; Dong et al., 2004; Dube et al., 2001; Dube, Anda, Felitti, Edwards, & Croft, 2002; Dube et al., 2005; Dube et al., 2003; Edwards, Holden, Felitti, & Anda, 2003; Felitti et al., 1998; Hillis et al., 2004; Whitfield, Anda, Dube, & Felitti, 2003). For example, individuals reporting four or more categories of childhood adversities had four- to 12-fold greater risks for life-threatening psychiatric disorders (Fergusson, Horwood, Grant, & Ridder, 2005b), and a higher incidence of overlapping disturbances of both physical and mental health (Anda et al., 2006). The robust dose-response relation between ACE scores and patient health led many authors to argue for the inclusion of childhood history within routine medical examinations, and has caused researchers to probe further into how ACE may be translated into behaviour problems and poor health.

In the midst of widespread attention, the ACE study has also been criticized for its reliance on retrospective reporting of exposure to ACE prior to the age of 18. Those critical of the study charge that participants may not have produced reliable reports of their childhood histories due to forgetting or bias, and that the findings from the study could be biased due to the fact that those who are suffering from poor health may be more likely to report exposure to adversity early in life. Skeptics have also questioned the absence of a clear model detailing how early experiences lead to developmental health problems. The large age period covered in the ACE study also made it difficult to isolate the role of the early years in developmental processes.

These limitations could potentially alter the magnitude of associations observed between events and later morbidities as reported in the ACE study (see: (Widom, Raphael, & DuMont, 2004) and (Hardt & Rutter, 2004)). This panel shares these concerns, but the ACE study is highlighted here because of its importance in raising awareness of the issue. To address concerns regarding biases in the retrospective reporting of childhood experiences in the ACE study, we turn to prospective large-scale epidemiological studies, i.e., studies that have assessed adversity in childhood and then followed individuals across the life course to evaluate the long-term outcomes of exposure.

2. Evidence from prospective longitudinal studies

There is an extended body of prospective longitudinal studies revealing that ACE predict both immediate and long-term negative outcomes for children, thus suggesting that ACE Study associations are unlikely to be entirely accounted for by biased or selective recall of childhood events. For example, the *National Longitudinal Study of Adolescent Health* (Add Health) was started in 1994 and followed a nationally representative sample of adolescents (in grades 7 thru 11) into young adulthood via in-home assessments. A sub-analysis of the study (n=12,748) found that all types of, or combinations of types of, maltreatment were strongly associated with

adolescent binge drinking; again these predictions held after controlling for key factors such as age, gender, race, parental alcoholism and monitoring (Shin, Edwards, & Heeren, 2009). Findings from the Add Health study have also demonstrated that experiencing maltreatment approximately doubles the probability of engaging in a number of different types of crime (Currie & Tekin, 2006).

Findings from the *1958 British Birth Cohort Study*, a 45-year prospective study of 98% of all births occurring in one week in England, Scotland, and Wales, documented robust associations between exposure to adversities, defined here as exposure to traumatic events or stressors prior to age 16 (including illness, parental absence, parental divorce, physical abuse, neglected appearance and sexual abuse) and psychopathology during adolescence, early adulthood *and* mid-life (Clark, Caldwell, Power, & Stansfeld, 2010). Remarkably, most of these associations did not attenuate with age as cumulative adversity, sexual abuse and physical abuse prior to age 16 continued to predict psychopathology in mid-life. A combined analysis of the 1958 and 1970 British Cohort studies also supports the longstanding observation of the graded and independent association been childhood SES and adult mental health (Mensah & Hobcraft, 2008).

The Avon Longitudinal Study of Parents and Children (ALSPAC) is another important cohort study of children from the United Kingdom where early adversity was documented from pre-birth onwards (Avon Longitudinal Study of Parents and Children (ALSPAC)). In ALSPAC, early exposure to family adversity and life stress was also found to predict behaviour problems later in childhood (Enoch, Steer, Newman, Gibson, & Goldman, 2010). Another report also showed that maternal depression partly accounted for children's early exposition to family adversity, but that these risk exposures predicted clinically diagnosed conduct problems controlling for maternal depression (Barker, Copeland, Maughan, Jaffee, & Uher, 2012).

As suggested by the ACE study, the negative outcomes associated with early adversity also extend to physical health problems. For example, the 1958 British Birth Cohort study has linked adversities within parent-child relationships to obesity and type 2 diabetes at 45 years of age (Thomas, Hypponen, & Power, 2008), and the European Prospective Investigation into Cancer has produced evidence that difficulties and life events experienced in childhood are prospectively associated with poorer functional physical health in adulthood (Surtees & Wainwright, 2007).

A quartet of prospective longitudinal studies stands out in terms of the breadth and quality of their follow-ups, and their ability to trace the effects of early adversity on later mental health and behaviour. The *Dunedin Multidisciplinary Health and Developmental Study* has provided compelling illustrations of how exposure to childhood adversity predicts criminality, poor mental health and substance use well into young adulthood [Details of the Dunedin Study can be found in Textbox 2.1]. Recently, Danese and colleagues (Danese, 2009) provided evidence that children in the Dunedin Study who were exposed to ACE, namely, socio-economic disadvantage, maltreatment (including maternal rejection assessed at age three, harsh discipline assessed at ages seven and nine years and exposure to physical and sexual abuse reported when they reached adulthood[2]) and social isolation (defined here as tending to do things on his/her own and being

[2] Current work on the 1958 British Birth Cohort (personal communication from Power, Thomas, Li, and Hertzman) suggests that retrospective reappraisal bias, based upon ones current mental state, is not as large a problem as previously thought. Because of the ethical and methodological problems of obtaining childhood reports of extreme

'not much liked by other kids') were at an increased risk for major depression at age 32. Each type of early adversity predicted later depression, with rates of depression increasing in synchrony with the number of adversity factors. Children exposed to early adversity remained at risk for depression in adulthood even after controlling for a number of common risk factors.

As detailed in Textbox 2.1, the *Christchurch Longitudinal Health and Development Study* has also tracked children from birth into mid-life. Although retrospective reports of physical punishment and maltreatment were obtained at age 18, the prospective assessment of mental health problems allows for an examination of the association between adversities reported to occur during childhood and early adolescence, and later mental health. Findings from this study indicate a strong association between maltreatment and later criminal offending, substance use and mental health problems (Fergusson & Lynskey, 1997). Although part of the longitudinal association was explained by social and contextual factors, exposition to harsh or abusive parenting remained robust and independent predictors of violent offending, suicide attempts, being a victim of violence, and alcohol abuse at age 18.

In Canada, a series of prospective longitudinal studies of kindergarten children initiated in Québec in the early and mid-1980s, have also documented the longitudinal associations between early experience and developmental trajectories, and later negative outcomes (see Textbox 2.1). These studies typically took advantage of multiple assessments over time to more finely characterize developmental trajectories that children followed, and identify experiences and factors in the family that predicted children's development and life outcomes. Findings from these studies revealed that trajectories of behaviour problems during the elementary school years—which were strongly associated with adverse childhood (familial) experiences—significantly predicted violent and non-violent antisocial behaviours, substance abuse, and suicide attempts in adolescence (Brezo, 2008a; Brezo et al., 2008b; Côté, Zoccolillo, Tremblay, Nagin, & Vitaro, 2001; Dobkin, Tremblay, Mâsse, & Vitaro, 1995; Fontaine et al., 2008; Mâsse & Tremblay, 1997; Tremblay, 1994).

But, more importantly for the questions posed in this chapter, the problematic developmental trajectories revealed in the two Quebec studies were associated with concurrent adverse familial factors (i.e., teen-age parenting, single parenthood, low parent education and SES), poor parenting (i.e., harsh-punitive parenting and lack of supervision), and childhood abuse assessed retrospectively (Brezo, 2008a; Brezo et al., 2008b; Haapasalo & Tremblay, 1994; Nagin & Tremblay, 2001). These associations suggest that the *interplay* between familial adversity and the developing child's personality factors may play an important role in the development of subsequent negative outcomes. At present, it is unclear the degree to which adverse experiences in the family *per se* serve as independent determinants of negative outcomes, as compared to the contribution of this dynamic interplay of child and circumstances.

---

early adversities, adult reports may be the most valid way to supplement prospective information on the conditions of early life.

Textbox 2.1. A unique quartet of prospective longitudinal studies

The Dunedin Multidisciplinary Health and Development Study *is one of the longest running studies of psychiatric disorders and health in the world (Dunedin Multidisciplinary Health and Development Research Unit). The cohort of 1,037 children (52% male) was constituted at three years of age, when investigators enrolled 91% of consecutive eligible births between April 1972 and March 1973 in Dunedin, New Zealand. Follow-up assessments were conducted at ages five, seven, nine, 11, 13, 15, 18, 21, 26 and 32 years of age, when 96% of the living Study members were assessed in 2003-2005. For each phase, the Dunedin Study members return from all over the world to the research unit for a detailed assessment of virtually all aspects of their physical and mental health, including measures of cardiovascular, dental, respiratory, sexual and mental health, psychosocial well-being, and detailed interviews about their relationships, behaviour and family. Just over 300 miles away in Christchurch, another birth cohort of over 1200 New Zealanders has been followed from their birth in 1977 into adulthood (University of Otago). The children in the cohort were assessed at birth, four months of age, one year and at annual intervals to age 16; thereafter, cohort members were assessed at ages 18, 21, 25 and 30. Data collection for the study was based on a multiple informant design, with parents, teachers and study members providing information on life histories and experiences. Similar to the Dunedin Study, archival information such as hospital records and police record data was also examined. The* Christchurch Study *has also helped to build the evidence base linking early experiences of harsh parenting, maltreatment and SES to a wide range of outcomes in adolescence and young adult. The* Montréal Longitudinal and Experimental Study *was initiated in 1983 as a longitudinal study of 1,037 kindergarten boys from low socioeconomic areas of Montreal (GRIP Research Unit on Children's Psychosocial Maladjustment). The boys and their families were assessed annually from six to 17 years of age, and then at 20, 24 and 28 years of age, through parents, teachers, classmates, and self-ratings, through standardized hormonal, physiological, neuropsychological, and psychiatric interviews, as well as through data from official files: birth records, achievement and services record, social services, and juvenile courts. The* Montréal Longitudinal and Experimental Study *also included the first intensive (two years) multi-modal (parent training, social skills training, teacher support) randomized experimental preventive intervention for disruptive children, which has shown long-term positive effects on a number of outcomes (school completion, delinquency, violence, substance use). Quite along the same lines, the* Québec Longitudinal Study of Kindergarten Children (QLSKC) *followed a sample of 3,018 children, representative of the boys and girls who attended kindergarten in a Francophone public school in Québec in 1986-87 and 1987-88 (CHU Sainte-Justine Research Center & Clinical Research Unit on Children's Psychosocial Maladjustment* and *GRIP, Research Unit on Children's Psychosocial Maladjustment). Kindergarten and elementary school teachers, as well as mothers, yearly assessed the behaviour of all the children in their classrooms from 6 to 12 years of age. Self-reports were then used at 15, 21-22, and 26-28 years of age. Structured psychiatric interviews were conducted at 15 and 21-22 years of age, and data were collected from official files. Parenting behaviours were assessed early, and official data on abuse and neglect were collected from social services and youth courts. Blood samples allowing for genotyping were also collected.*

Taken together, these four studies have provided compelling evidence for the importance of childhood experiences for a wide range of life outcomes. In addition to the British cohort studies and the four studies profiled above, a number of other birth cohort studies have also demonstrated a robust association between early adversity and the development of mental health problems across adolescence and into adulthood. For example, results from 1089 of the 4140 births enrolled in the Providence, Rhode Island cohort of the *National Collaborative Perinatal Project* indicate that childhood adversity (including low SES, family disruption, and residential instability assessed at age seven) predicts the onset of depression, both in childhood and in adulthood, as well as poor prognosis for the disorder (Gilman, Kawachi, Fitzmaurice, & Buka, 2003). More specifically, childhood adversity was found to increase the risk of recurrence of depression and reduce the likelihood of remission. The work of Hammen and colleagues (Hammen, Henry, & Daley, 2000; Hazel, Hammen, Brennan, & Najman, 2008) in Australia has also shown how early stressors can foreshadow the onset of clinical depression in adolescence and young adulthood.

Relatively large cohorts of 'at-risk' children have also been followed over time to test whether the relation between childhood adversity and poor mental health outcomes holds among these vulnerable subpopulations (e.g., low SES children; see (Haapasalo & Tremblay, 1994; Mâsse & Tremblay, 1997)). Collectively, these studies illustrate that the *severity* of early life experiences (including maltreatment, socio-economic deprivation, care giving disruptions, and harsh parenting) predict difficulties in adult life even among populations where the majority of children have experienced at least one form of early adversity. For example, studies that have followed court-involved children and adolescents into late adolescence and early adulthood have consistently demonstrated that childhood maltreatment, including both physical abuse and neglect, remains a robust predictor of behavioural problems and mental health symptoms in young adulthood (see for example work by (Kaplow & Widom, 2007); and for meta-analytic results from justice-involved and delinquent populations see (Loeber & Farrington, 1998)). Similarly, the Project on Human Development in Chicago Neighborhoods has demonstrated that, even within at-risk neighborhoods, the degree of exposure to family conflict early in life predicts substance use disorders and externalizing problems during late adolescence and emerging adulthood (Skeer, McCormick, Normand, Buka, & Gilman, 2009).

Starting in 1955 on the island of Kauai, Hawaii, a 40-year study followed a multi-ethnic cohort of 698 children born with multiple risk factors: biological, economic, and family functioning (Werner, 1997). These children were assessed during childhood at age 1, 2, and 10, then followed up in adolescence, age 28 and 40. Approximately two-thirds of the group developed criminal or mental health problems, a proportion clearly above what would be expected in the general population. Interestingly, approximately 30% did not develop these problems, despite multiple early risk factors. They shared a variety of characteristics, including a positive temperament and self-esteem, and good reading skills. Most important, however, was their capacity to find alternate mentors outside their immediate family, such as grandparents, teachers, scout leaders, etc. who treated them as special and provided them with guidance and mentorship during their formative years (Werner & Smith, 1989). The Kauai study was thus instrumental in pointing to the importance of personal and social resilience factors that, in the context of complex at-risk environments, may protect at-risk children from following problematic trajectories.

Thus, by and large, studies from 'at-risk' populations illustrate that the severity and cumulative impact of early adversity predicts long-term developmental health outcomes, even when children are embedded in families and neighborhood contexts where exposure to adversity is the norm. However, it should be emphasized that these predictive associations are clearly probabilistic, with a significant number of at-risk children not falling on these negative trajectories due to protective factors.

From a scientific perspective, it is promising that a consistent set of findings linking early adversity to young adult outcomes is emerging from both representative and high-risk populations. However, the presence of robust longitudinal associations between early adversity and child outcomes alone is not sufficient to conclude that early adversity is the *cause* of later suffering. To help identify the ways in which early adversity may influence children's later lives, we now turn to the new generation of cohort studies that have an increased resolution of

assessment during the early age combined with unique design features that, in some cases, allow for stronger tests of whether and/or how exposure to adversity early in life influences the developing child.

a. What can the new generation of longitudinal studies tell us about the influence of early adversity on children's development?

Although recently established cohort studies cannot yet tell us whether the effects of early adversity persist into young adulthood, they illustrate how early life experiences place children on pathways toward poor adult outcomes by increasing the risk for substance use difficulties, behavioural problems and mental health problems during adolescence. Prediction of later delinquency by early physical aggression and oppositional—defiant behaviours has indeed been confirmed for boys, but not for girls, in a cross-national study based on longitudinal data collected in six major cohorts, including the two Quebec studies referenced earlier (Broidy et al., 2003). Interestingly, some of these predictions varied as a function of the type of behaviour problem. For example, chronic oppositional problems during elementary school led to covert delinquency (theft) only, whereas chronic physical aggression during elementary school led to violent delinquency (Nagin & Tremblay, 1999), suggesting the persisting role of underlying personality factors, such as self-control and regulation, in the developmental process leading to different forms of delinquent behaviours. These results were replicated in recent analyses of data from the Dunedin study (Moffitt et al., 2011), showing that self-control during the elementary school years predicts in a gradient-like form poor physical health, substance dependence, criminal conviction, as well as family and financial direness at age 32, over and above social class, IQ and family effects. Similar findings have also been reported concerning a wide range of adult outcomes, including depression, substance use disorders, self-harm behaviours, poor educational outcomes, physical health problems and dependence on social welfare systems (Fergusson, Grant, Horwood, & Ridder, 2005a; Kim-Cohen et al., 2003; Kratzer & Hodgins, 1997; Moffitt, Caspi, Harrington, & Milne, 2002; Wiesner, Kim, & Capaldi, 2005).

Thus, it seems that early experiences reach into young adulthood by placing children on a specific pathway at an early age/during a critical period. The identification of early emerging mental health problems is important given that an estimated 50% of adults with a psychiatric disorder have been shown to have had a diagnosable disorder (typically conduct disorder) between the ages of 11 and 15 (Kim-Cohen et al., 2003).

New cohort studies are also positioning themselves to answer *how* early life experiences may influence the lives of children, often by integrating novel features to help determine whether early adversity plays a causal role in children's development. These studies are important to consider as they provide a finer grained resolution of the early life experiences of children alongside state-of-the art assessments of biological, familial and social factors. Many of these studies also leverage 'natural experiments' (e.g., twin and adoption studies) to help answer the question of whether exposure to early adversity is a cause—versus associated risk—of poor adult outcomes.

ACE have already been shown to predict a wide range of early emerging mental health problems and childhood difficulties among these more recent cohorts. For instance, the *Quebec*

Longitudinal Study of Child Development (QLSCD) (Institut de la statistique du Québec) and the *Quebec Newborn Twin Study (QNTS)* (Boivin et al., (in press). The Quebec Newborn Twin Study into adolescence: 15 years later. *Twin Research and Human Genetics*), its companion study, are two large scale Canadian studies initiated in the late 1990s that have prospectively followed a large sample of infants (N=2120 single-born infants sampled to be representative of the population of infants born in the province of Québec, and 1324 twin infants respectively). Beginning at five months of age and then yearly, the children and their families were assessed on a variety of personal, family and social-environmental characteristics, including extended and detailed assessments of proximal (e.g., parenting behaviours) and distal (e.g., family income) features of the child's environment across development. They are thus well positioned to assess how children's development may be shaped by interactions between the child and a wide range of early adverse experiences with in communities, schools and families.

Recently established cohort studies are still in their infancy, with most having examined in various ways how early exposures to adversity predict developmental trajectories of early behaviour characteristics. By and large, the reports on these studies tell a similar story underlying the importance of early ACE: (1) individual differences in terms of developmental trajectories of problem behaviours are established very early in life, (2) they are predicted by a host of prenatal and perinatal factors reflecting early environmental adversity, such as low family income, being exposed to maternal smoking during pregnancy, lifetime and postnatal depressive symptoms experienced by the mother and the father, low parental self-efficacy, harsh parenting, and family dysfunction; (3) early adversities, such as low SES, family dysfunction, and harsh parenting, are often enduring and interacts with child factors (e.g., difficult temperament, low self-control) in predicting later behaviour problems and a cascade of negative circumstances, such as peer difficulties, paving the way to later adjustment problems (Côté et al., 2009; Huijbregts, Séguin, Zoccolillo, Boivin, & Tremblay, 2008; Leblanc et al., 2008; Petitclerc, 2009; Petitclerc & Tremblay, 2009; Pierce et al., 2010; Vitaro, Barker, Boivin, Brendgen, & Tremblay, 2006).

For example, a range of maternal and family variables assessed before birth were found to predict high physical aggression trajectories during early childhood (Tremblay et al., 2005). These predictors include mother antisocial behaviour during adolescence, giving birth before 21 years of age, not having finished high school, smoking during pregnancy, parent separation before birth and low income. After controlling for these prenatal predictors, family dysfunction and maternal coercive-hostile parenting at five months also added to the prediction of high physical aggression. These results point to a combination of environmental determinants involved in the early signs of adjustment problems. However, using the same assessment of physical aggression, QNTS also showed that as early as 17 months, and at least up to age six years, inter-individual differences in frequency of physical aggression is also accounted for by genetic factors (Dionne, Tremblay, Boivin, Laplante, & Pérusse, 2003; Van Lier et al., 2007), thus raising the possibility of gene-environment interplay accounting for these predictive associations. Furthermore, highly physically aggressive toddlers, as well as those exposed to hostile reactive parenting and to low income families at 17 months of age, were more likely to experience chronic peer relation difficulties in the preschool years (Barker et al., 2008), a social context likely to entrench their behaviour problems and entrap them in a deviant pathway. Thus, the early developmental pathways appear intricate and subjected to many genetic and environmental factors interacting over time.

Likewise, the *Environmental Risk (E-Risk) Longitudinal Twin Study* prospectively assessed the biological, familial and social risk status among a 1994-95 birth cohort of 2232 twins living across Britain. The E-Risk study is well positioned to test how various experiences across settings interact to alter children's mental health trajectories. For example, findings from the E-Risk Study indicate that children who experienced maltreatment by an adult (assessed retrospectively and prospectively at ages five, seven, ten and 12) were more than three times as likely to report psychotic symptoms at age 12 than were children who did not experience such traumatic events. The risk associated with childhood trauma remained significant in analyses controlling for children's gender, socioeconomic deprivation, and IQ; as well as for children's early symptoms of internalizing or externalizing problems; and for children's genetic liability to developing psychosis (Arseneault et al., 2011)**.** Results from the E-Risk study have also illustrated how exposure to neighborhood-level poverty predicts antisocial behaviour across the elementary school years. On the positive side, this study also provided evidence that the level of collective efficacy in a community (that is, how well people in a neighborhood know each other and how willing they are to intervene when needed) buffered the effects of poverty on children's antisocial behaviour at school entry (Odgers et al., 2009).

Both the E-risk study and the QNTS are genetically informed studies that provide an opportunity to test for possible gene-environment interplay in developmental trajectories. The rationale and possibilities offered by these studies are reviewed in Textbox 2.2.

Textbox 2.2. The contribution of genetically informed studies

Rationale for twin studies: *Showing a correlation between an early environmental risk factor (e.g., harsh parenting, maltreatment) and a child outcome (e.g., behaviour problems) using traditional family studies is of limited value because environmental and genetic factors are confounded (Turkheimer & Gottesman, 1996). Clearly, an association, even if predictive (i.e., longitudinal), is not sufficient to establish a causal link. Concluding that a factor, such as maltreatment, is the cause of future mental health suffering is a challenging task. The gold standard for establishing a causal relation would involve conducting an experiment where children would be randomly assigned to experience the maltreatment or not; for obvious reasons random assignment to ACE is neither ethical nor desirable. Over the last decade, a number of quasi-experimental and genetically informed studies have followed children longitudinally starting in their early years and have attempted to address whether it is exposure to early adversity* per se *(versus other confounding factors such as shared parent-child propensities) that places children at heightened risk for developmental problems, such as criminal behaviour, mental health problems and/or substance abuse and dependency. Here, we highlight findings from studies that, next to experiments, provide some of the strongest controls in assessing the role of environmental risk factors in future developmental health.*

Twin and adoption designs offer the advantage of providing estimates of both genetic and environmental sources of variance and can serve as quasi-experimental tests of environmental theories (Rutter, 2007). The twin design allows for a statistical estimation of genetic versus shared and non-shared environmental sources of variation for a given phenotype (i.e., an observable characteristic or trait) by comparing the phenotypic similarity among identical (monozygotic) twins, who share 100% of their genes, to that of fraternal (dizygotic) twins, who share on average 50% of their genotype. Higher phenotypic similarity favoring identical versus fraternal twins is assumed to reflect genetic sources of variance (i.e., heritability), whereas equivalent or low phenotypic similarity across levels of genetic relatedness (i.e., identical versus fraternal) represents shared (or family-wide) and non-shared (or child-specific) environmental sources of variance.
The additive genetic model of genetic and environment sources of influence described above has its limitations: (1) genetic and environment estimates are crude approximation prone to error, sensitive to methodological factors, and may vary across situations (Turkheimer & Gottesman, 1996), (2) the model is not consistent with new findings showing that G x E contributions are non-independent (but see below), (3) it does not specify which genes are involved, (4) the estimates do not ascertain the causal properties of genes and environment (only interventions

and experiments may do so;(Turkheimer, 2011)), but rather help refine promising pathways for additional causal investigation. Indeed, the basic strength of twin studies lies in their capacity to document within-family similarities and differences, something that studies of singletons cannot do, and then show when genes matter and when environments matter for further exploration.

Yet, teasing apart environmental and genetic sources of variation may provide a useful form of statistical control for genetic factors when estimating the putative contribution of adverse childhood environment to developmental trajectories. For example, in QNTS, preschool cognitive school readiness was more strongly accounted for by environmental factors shared and uniquely experienced by children of the same family than by genetic predisposition (Lemelin et al., 2007). This environmental mediation also extended to the prediction of school achievement in the early school grades, as well as to the family processes (i.e., early literacy training by parents) underlying the link between SES and school readiness (Forget-Dubois et al., 2009).

When specific environments are directly measured, twin studies may also signal possible gene-environment interplay in developmental trajectories. Indeed, the twin method is usually applied to the study of individual phenotypes, but its rationale can be extended to studies of measured environments, such as various ACE (e.g., harsh parenting), to estimate the extent to which measured features of ACE are shared or uniquely experienced by twin siblings, and whether they are associated with genetic factors in the child. Following the same logic, the approach can be extended to predictive associations between a feature of the environment and a developmental outcome in the child, thus providing a way to play out alternative scenarios when testing the extent to which predictive associations are environmentally mediated (for examples see (McGue, Osler, & Christensen, 2010)).

Maltreatment and anti-social behaviour: *Accordingly, Jaffee and colleagues (Jaffee et al., 2005; Jaffee et al., 2004a; Jaffee, Caspi, Moffitt, & Taylor, 2004b) leveraged a genetically informative research design to test the hypothesis that physical maltreatment plays a causal role in the development of children's antisocial behaviour and exerts an effect that is, at least partially, due to environmental exposures. Alternative explanations are that the association between early maltreatment by caregivers and children's behaviour problems can be attributed to a genetic propensity for antisocial outcomes shared by the parent and the child, or to the caregiver reacting to a child characteristic under genetic influence (see (Boivin et al., 2005)). This type of confound is referred to as a gene-environment correlation, meaning that gene variants become associated with risk exposures through children's characteristics or children's and parent shared genes (Jaffee & Price, 2007). Data was drawn from the* Environmental Risk (E-Risk) Longitudinal Study, *described above, to study the relationship between child maltreatment (as reported by mothers) occurring before the age of five years and children's antisocial behaviour at five and seven years. The analyses provided four pieces of evidence that were consistent with a causal relationship between children's experiences of maltreatment and their antisocial behaviour: (1) physical maltreatment experienced prior to age five predicted increases in antisocial behaviour during childhood, (2) there was a dose-response relationship between the severity of physical maltreatment and the severity of children's antisocial behaviour problems, (3) genetic factors accounted for a small and statistically non-significant portion of the variance in physical maltreatment, suggesting that genetically-influenced characteristics of children were not provoking an abusive response from adults, and (4) physical maltreatment was uniquely predictive of children's antisocial behaviour after controlling for parents' antisocial behaviour, although the magnitude of the association was reduced. Point (3) above was nuanced by findings from the Quebec Newborn Twin Study showing that exposure to harsh-reactive parenting at five months was partly associated with the infant genotype through the infant's difficult temperament (Boivin et al., 2005). However, this pattern was not maintained when harsh parenting was examined longitudinally from five months to 30 months (Forget-Dubois et al., 2007), thus pointing to the transient nature of the genetically mediated child "effects" at five months.*

By and large, the results from genetically informative research designs, summarized in Textbox 2.2, suggest that the contribution of ACE, specifically maltreatment and harsh parenting, to developmental health is, at least in part, environmentally mediated. However, the evidence regarding substance use and abuse (or addiction; we use these terms interchangeably as they both implicitly refer to a problem of clinical significance, whereas substance use points to a degree of consumption) as a developmental outcome is not as conclusive and calls for further clarifications and nuances.

b. The case of substance use/abuse

The last fifteen years of research on substance use/abuse has indeed increased our knowledge base on the genetic and environments determinants, as well as on the neurobiological underpinnings of various dependencies. This knowledge base now points to a series of defining features of addictions. First, addictions clearly imply identified brain pathways and systems, such as the dopamine systems, in dependence, and these systems both affect and are affected by substance use (Koob & Volkow, 2010). Second, the contribution of genetic factors to substance use/abuse is substantial for alcoholism and for cocaine and opiate addiction (Goldman, Oroszi, & Ducci, 2005); gambling problems, now considered as an addiction by the American Psychiatric Association, also shows a similar pattern (Slutske, Zhu, Meier, & Martin, 2010). Third, there are substantial co-occurrences across various forms of addictions and these co-occurrences are associated to a significant degree to a set of common genetic factors, suggesting that a shared set of biological vulnerabilities could underlie a more general addiction syndrome (Wareham & Potenza, 2010). It has been suggested that behavioural disinhibition, an inability to inhibit undesirable actions partly due to a lack of cognitive control, to impulsivity and to sensitivity to reward, is one such underlying genetically liable factor (Iacono, Malone, & McGue, 2008). Fourth, early adversities, such as having been exposed prenatally to alcohol and nicotine, low SES, and maltreatment, have been associated with substance abuse. However, the developmental processes underlying this prediction are not clear. Genetically informed studies have generally failed to document an environmental pathway linking addictions and behaviour problems across generations. For example, using data from the Vietnam Era Twin Registry, Haber, Jacob and Heath (Haber, Jacob, & Heath, 2005) showed that the genes common to alcoholism and conduct problems accounted for the intergenerational association between these two problems. Waldron and colleagues (Waldron, Martin, & Heath, 2009) found little evidence of environmental transmission of risk from parental alcoholism to antisocial behaviour in two ongoing Children of Twins studies in Australia. Adoption studies have also failed to show a predictive association between the adoptive parents alcohol use and alcohol disorders among the offspring (see for example: analyses from the Danish (Goodwin, Schulsinger, Hermansen, Guze, & Winokur, 1973), Stockholm (Cloninger, Martin, Guze, & Clayton, 1985) and Iowa adoption studies (Cadoret, Troughton, & O'Gorman, 1987)). Thus, although relatively small in number, genetically-informed studies have produced relatively consistent findings pointing to the lack of an environmental contribution of parental alcoholism to the offspring's alcohol-related disorders (for a review see (Slutske et al., 2010)) and antisocial behaviour.

These features clearly point to some form of genetic liability pathway to addictions. However, they should not be seen as the end of the story, and some of these findings should be qualified. For instance, the high heritability of addictions should not be seen as fixed entities. For instance, they may not apply to specific societal groups, such as First Nations where the multiple stresses associated with acculturation may override genetic influence, or in contexts (e.g., rural or religious settings) where the environment may constraint individual choices (Koopmans, Slutske, van Baal, & Boomsma, 1999; Legrand, Keyes, McGue, Iacono, & Krueger, 2008; Rose, Dick, Viken, Rj, & Kaprio, 2001); see also (Iacono et al., 2008). The developmental period (i.e., age of the child) is also an important actor in that respect. For instance, a small number of twin studies showed that in early adolescence, when adolescents start experimenting with substance use (i.e., initiation), environmental factors shared by twin of the same family are significant, before giving

way to genetic and non-shared environmental influences in late adolescence (Hopfer, Crowley, & Hewitt, 2003; Lynskey, Agrawal, & Heath, 2010; McGue, Elkins, & Iacono, 2000; Schmitt et al., 2008). Thus, exposure to family-wide and child-specific environmental risks during that transitional period (e.g., lack of parental supervision; substance availability, affiliation with peers) could further increase the risk of addiction generally, as well as specifically (i.e., with respect to a specific substance). It is not clear if the role of these environmental risks could be traced back to early adversity. Finally, as will be discussed later in the chapter, these high heritability figures could hide the role of environment in more complex gene-environment transactions, such as G-E correlations and G x E interactions in development (see below). G-E correlations are likely because children at-risk for some genetic reason (e.g., a genetic liability for behavioural disinhibition) could evoke or actively select risky environments (e.g., where substance are more available). G x E interactions are also likely because substance use/abuse could be conditioned by a genetic propensity and an environmental context (e.g., that facilitates substance use. These G-E transactions are only starting to be documented in longitudinal research.

Finally, another decisive piece of evidence pointing to the causal (environmental) role of ACE comes from a series of preventive interventions designed to mitigate the negative impact of these ACE.

c. Changing developmental trajectories through randomized preventive trials

As discussed earlier, the norm for establishing causality is a true experiment whereby children would be randomly allocated to various conditions of adverse experiences. For obvious reasons these experiments do not exist. However, there are a few well-documented preventive trials, some of which are covered in Chapter 5 where "at risk" children were exposed, in some cases through randomization, to an enriched environment and then followed longitudinally.

The High/Scope (Perry) Preschool preventive intervention program, perhaps the best known of these programs, was an intensive intervention program, initiated in the mid-sixties, and aimed at three to four-year-old children (N = 123) of low IQ and from low SES backgrounds. The children were randomly allocated to a program group that received a high-quality preschool education program based on High Scope's participatory learning approach, or to a comparison group who received no preschool program. The children attended the preschool five half-days a week over a two-year period. The program benefited from a one to five/six staff-to-child ratio and included a weekly home-visit component. The children were then (and are still) followed longitudinally and assessed regularly at least up to age 40. The longitudinal evaluation revealed a range of long-term benefits for the children who attended the program, as compared with children from the control group. These developmental gains include higher rates of academic achievement, employment, and income, as well as a significantly lower rate of crime and delinquency, lower incidence of teenage pregnancy and welfare dependency (Nores, Belfield, Barnett, & Schweinhart, 2005).

First initiated as a longitudinal study of boys from low socioeconomic backgrounds, the *Montréal Longitudinal and Experimental Study* also included a two-year randomized experimental preventive intervention aimed at seven-year-old disruptive boys drawn from a

community sample (N = 250). These 250 boys were randomly assigned to an intervention group or to one of two control groups (attention–control and control groups). The intervention program was multi-modal and involved social skills training, parent training, and teacher support. The children have been followed longitudinally up to age 24. Compared with children from the control groups, children who benefited from the program were more likely to graduate from high school, less likely to report delinquent behaviours, to use illicit substance, and to have a criminal record at age 24 (Boisjoli, Vitaro, Lacourse, Barker, & Tremblay, 2007; Lacourse et al., 2002). An extension of this program, the Fluppy program, now well disseminated in Quebec, is actually the object of a current randomized trial for further evaluation.

Other randomized early prevention programs with extended follow-ups that were found to positively influence developmental trajectories include the Elmira Nurse Home Visitation program aimed at low SES young pregnant women (Olds et al., 1998, see Chapter 4), the Carolina Abecedarian program mainly aimed at improving school achievement (Burchinal, Campbell, Bryant, Wasik, & Ramey, 1997; Campbell, Ramey, Pungello, Sparling, & Miller-Johnson, 2002; Ramey et al., 2000), and the Incredible Years, although the follow-up in this case did not reach adolescence and early adulthood yet (e.g., (Webster-Stratton, Reid, & Stoolmiller, 2008)). There are also other evaluated programs (extended follow-up, but no randomized trial), such as Chicago Longitudinal Study of Child-Parent Centres (Reynolds, Walberg, & Weissberg, 2002; Reynolds, Temple, Ou, Arteaga, & White, 2011a; Reynolds et al., 2007), that were also proved to be effective in changing intellectual performance and school achievement of "at risk" children.

Many of these programs underwent economic analyses to show that that they are highly cost effective (Barnett & Masse, 2007; Nores et al., 2005; Reynolds, Mathieson, & Topitzes, 2009; Reynolds et al., 2011a; Reynolds et al., 2011b). The 'rate of return' estimates are often cited in favour of investing in preschool education programs. In some cases (i.e., High/Scope-Perry-Preschool), the magnitude of these estimates had to be revised toward the low end to take into account selective sample loss due to attrition. However, even these more stringent evaluations generally support the claim of a robust statistical, albeit more modest than previously heralded benefit-to-cost ratio (Heckman, 2006).

Although few in numbers, these prevention studies converge in showing that an experimentally induced enriched environment may have long-term protective effects for 'at-risk' children, thus benefiting both the individuals and society. On a larger scale though, such as trying to move families out of poverty or, more globally, ameliorating their socioeconomic conditions through policies and programs, the evidence has been mixed. Previous creative natural experiments had demonstrated marked improvements in children's conduct symptoms when their family was lifted out of poverty (Costello, Compton, Keeler, & Angold, 2003). Yet, randomized housing experiments have generated mixed support regarding whether movement from a deprived neighbourhood can reduce children's levels of behavioural problems (Kling, Ludwig, & Katz, 2005).

Thus, there is converging evidence from both longitudinal studies and early intervention trials that ACE are causally involved, through environmentally induced processes, in negative developmental trajectories. Most importantly, these early prevention trials and their follow-ups

also demonstrate that intervening early through appropriate programs may change developmental pathways, especially if the intervention is aimed at the child and his/her proximal environment (see also Chapter 5).

In the next section, we review new evidence highlighting the role of gene-environment transactions in building individual differences in developmental trajectories. If there is a lesson to be learned from genetically informed research in the last ten years, it is that models positing an independence of genetic and environment determinants are generally over-simplifying reality, and that inferences that separates genes and the environment are fast being superseded by our emerging understandings of gene-environment interplay.

3. Individual differences in developmental trajectories: the role of gene-environment interplay

As described in Textbox 2.2, a number of assumptions underlying the independent, additive genetic model of heritability and environment factors have been criticized, including the postulate that genetic factors and environmental factors act independently. More than 40 years ago, Donald Hebb, a well-known psychologist was asked the question, "What is more important to human personality, nature or nurture?" His now famous reply can be paraphrased as: "What is more important to a rectangle, the length or the width?" (Meaney, 2001). This inspired response really says it all. For too many years, the overly simplistic nature-nurture dichotomy has shrouded the important and complex interactions between genes, environment, and development, and limited our ability to investigate gene-environment interdependencies. Moving on is long overdue.

Accordingly, the contemporary approach for studying the origins of individual differences has successfully moved beyond the limited perspective of the long-evoked, but sterile "nature – nurture controversy" to examine the actual interaction between these two very real sources of variation. This perspective builds upon the research with non-human subjects (Meaney, 2010; Sokolowski, 2001; Sokolowski, Disma, & Abramson, 2010) demonstrating that the effects of an environment can only be understood when the genetic make-up of the individual is also considered (and vice versa). In other words, the same environment may have dramatically different effects on individuals depending upon their genetic make-up. Likewise, the same genetic make-up can produce dramatically different effects on outcomes depending upon the environment. This is what is meant by gene-environment interaction.

In the last 10 years, this position has successfully been integrated into longitudinal-epidemiological research, resulting in a corpus of results that dramatically changed our understanding of developmental psychopathology. Research designs that assess genetic factors directly, through specific markers, or indirectly, through twin and adoption designs, have started to document how gene-environment interplay shape the propensity for complex behaviours, such as those involved in mental health, criminality and substance use.

'Gene by environment' studies are shedding new light on how early stressors may lead to mental health and behaviour problems for some children and not others. For example, Avshalom Caspi and Terrie Moffitt's research team used data from the Dunedin Multi-disciplinary Health and

Development Study to provide some of the first evidence of how environmental factors such as early abuse and life stressors interact with a genetic vulnerability to increase the risk for future involvement in antisocial behaviour and depression (Caspi et al., 2002; Caspi et al., 2003). In a first paper published in *Science* (2002), they provided evidence that genetic variation in the gene encoding monoamine oxidase A (MAOA) accounted for why some children who were maltreated became violent offenders, while others did not (the study examined the effect among males only). MAOA is an enzyme that breaks down and helps regulate the neurotransmitters serotonin, dopamine, and norepinephrine in the brain. To a certain extent, these neurotransmitters govern the emotional and motor states and the individual tendency to actively look for cues in the environment. Simply put, they are the neurological substrates underlying the feeling of well-being and happiness, motivation, attention, learning and reward-driven activity. Although the MAOA genotype was not associated with later antisocial behaviour in general, males who had experienced maltreatment, and who also possessed the 'low activity MAOA allele', were more likely than high activity MAOA allele carriers to engage in antisocial behaviour and violence later in life. Boys with the low versus high activity allele were twice as likely to be diagnosed with conduct disorder, three times more likely to be convicted of a violent crime and were responsible for four times their share of violent crimes within the cohort (they were only 12% of the study group but they committed 44% of the crimes). A meta-analysis of seven studies testing this G x E interaction (Taylor & Kim-Cohen, 2007) supported these initial findings.

A second article provided the first evidence of a G x E interaction in the development of depression (Caspi et al., 2003). This time, a functional polymorphism in the promoter region of the serotonin transporter (5-HTT) gene—which codes for a protein that transports serotonin from the synapse into presynaptic neurons—moderated the prediction of depression in early adulthood by childhood and early adolescence stressful life events. Of children who inherited two copies of the short allele of the 5-HTT promoter polymorphism (the allele which makes less protein), 43% developed depression following four stressful life events, compared to 17% among people with two copies of the long allele.

This landmark study was transformative in that it generated research on how genes and environmental factors may interact to affect mental health (i.e., depression). It also became the object of intense scrutiny. A meta-analysis of 14 studies published in 2009 concluded that Caspi's original finding was not replicated (Risch, Herrell et al. 2009). Unfortunately a large body of the scientific evidence was ignored in this meta-analysis, including a number of positive replications of the original findings using well-controlled research designs. In addition, the reported effect sizes from the studies reviewed varied widely with the most weight given to studies with the largest number of participants, but in which information about life events and mental health was collected through weaker methods, (i.e., via phone surveys) rather than in person or through clinical assessments (see also (Uher & McGuffin, 2010)). A more complete meta-analysis of 54 studies helped to resolve this controversy by confirming a significant interaction between stressful life events and the 5-HTTLPR variant, and showing, as in Caspi's, that the interaction was highly significant when maltreatment was considered (Karg, Burmeister, Shedden, & Sen, 2011). This recent meta-analysis not only replicated the original findings that exposure to childhood maltreatment was particularly detrimental for individuals who are carriers of the short – S allele- of the 5-HTTLPR gene using a more complete set of studies, but it also illustrated that the interaction was strongest in studies that used in-depth interviews with subjects,

as opposed to questionnaires or phone interviews. The work by Karg and colleagues is especially important to consider for this review, not only because it illustrated the greater importance of serious chronic adversity versus acute negative life events, but also because it points to a biological risk process that begins in early childhood, although the outcome is assessed in late adolescence/early adult life (for a further discussion of these points, see also (Rutter, Thapar, & Pickles, 2009)).

This line of research suggests that exposure to early adversity may influence the expression of genes and, perhaps most importantly, illustrates that in the absence of environmental input a genetic predisposition may not be activated. Remember, in Caspi et al. (2001), the prediction by MAOA of antisocial outcomes was conditional: the 'risk allele 'conferred risk for antisocial behaviour *only* when the adverse environmental conditions (e.g., maltreatment experiences) were present.

Since these initial studies, there has been a rapid increase in the number of G x E interaction studies within psychology, psychiatry and related disciplines. These studies do not converge on a simple message and there is now a growing recognition of the complexity of these associations. For example, recent evidence suggests that the role of the MAOA genotype may interact in complex ways with the severity of trauma, age, and contextual factors, as well as differ for other forms of behaviour problems (McDermott et al., 2009; Tikkanen et al., 2009; Van Der Vegt, Van Der Ende, Ferdinand, Verhulst, & Tiemeier, 2009; Weder et al., 2009). Another case in point is the gene-environment interplay underlying the links between the serotonin-producing system and later psychiatric outcomes. For example, in the *Quebec Longitudinal Study of Kindergarten Children,* a 22-year follow-up investigation of the serotonin system's contribution to mood disorders and suicide attempts showed that five genes of this system were significantly associated in various ways with suicide attempts and mood disorders (Brezo et al., 2010). Some of these genes were associated with mood disorders and suicide attempts, whereas others were associated with suicide attempts only. Some of these links were direct, others, indirect through interactions with histories of sexual and physical abuse. Thus, despite their phenotypic association, mood disorders and suicide attempts may have divergent pathways, and it is important to identify and understand the various gene x environment interactions underlying these pathways.

G x E interactions are clearly pervasive, but the impact of all these interactions acting together on a given outcome and resulting in individual differences within a population, is still unknown. The studies described above show that the field has moved forward from testing G x E interactions solely on a one-to-one basis, but rarely in a real multivariate way (i.e., by examining all possible combination). We can now more fully appreciate the complexities of these associations, as well as the challenges of unravelling their significance for individual development. It is clear that the outcomes of interest in the present report are complex and influenced by multiple genes interacting with each other and interacting with multiple environments. However, the various G x E interactions do not necessarily pull development in the same direction, and we still do not know how they account for individual differences at the phenotypic end (i.e., the distribution in the population). The "new science" of development needs to further document these specific G x E interactions. The real challenge in the coming years will be to understand how these complex interactions act together in a meaningful way to lead to individual differences in adjustment. New developments in genetics, such as an increased capacity to ascertain multiple genetic factors

through Genome-wide association studies, are paving the way to a broader approach to assessing G x E interactions (see next chapter for more details).

On that note, it is interesting to signal that results pointing to gene-environment interactions were also revealed in twin studies where the contribution of the whole genotype rather than a single marker is estimated. For example, when examining the role of ACE in the early stress response, the interplay of ACE and genes was found to be significant, but to vary with age. Indeed, a complex pattern of time-dependent G x E interaction in the cortisol response was revealed (Ouellet-Morin et al., 2008; Ouellet-Morin et al., 2009). Family adversity, defined as cumulated risk factors such as low birth weight, smoking during pregnancy, and family poverty, was found to moderate the role of genes in the stress response, but in an age-dependant manner. At age six months, the role of genes (i.e., heritability) was found significant, but only in the presence of family adversity, whereas a reverse pattern was found at 18 months, i.e., genes played a significant role for the cortisol response in the absence of adversity, but not under adversity. This pattern suggests an evolving process of G x E interaction in the stress response across development. This pattern is quite consistent with a programming effect of the environment (possibly through parenting) superseding genetic influence at 18 months.

In another set of analyses, aggressive behaviours at school entry were significantly associated with befriending other aggressive children, but more so for children who were genetically at risk for aggression than for children who were not, thus supporting the finding that affiliating with aggressive friends is an environmental risk factor for aggressive behaviours operating according to G x E interaction (Brendgen, Vitaro, Boivin, Dionne, & Perusse, 2006; Van Lier et al., 2007).

4. Biological sensitivity to context: a non-specific form of gene-environment interaction

But what if instead of having a so-called specific genetic vulnerability enacted by a specific environment, some children were simply more biologically responsive to environmental context? An initially unanticipated observation has become the now recurrent finding, beginning with a 1995 report by Boyce and colleagues (Boyce et al., 1995), that children showing heightened stress reactivity in the laboratory display either the best or worst health outcomes, depending upon the level of adversity in their ambient social environments. Thus, highly reactive children in stressful school or home settings have the highest rates of illness, injury or behaviour disorders, while equally reactive children in highly nurturing, low stress homes have the lowest rates: lower even than their low reactivity peers. This observation has been interpreted as revealing a differential biological susceptibility to social context (see (Belsky, 1997; Boyce & Ellis, 2005; Ellis & Boyce, 2008; Ellis, Essex, & Boyce, 2005)), an evolutionarily conserved sensitivity to both the stressful and supportive characters of rearing environments. Such sensitivity to context appears to influence not only the rates and severity of morbidity but also the timing and pace of important developmental transitions, such as puberty (Ellis, Shirtcliff, Boyce, Deardorff, & Essex, 2011). As will be further described in Chapter 3, this characteristic, which likely becomes increasingly trait-like over the course of development (Alkon et al., 2006), appears to emerge as a 'conditional adaptation', garnering signals from the early social environment about the inherent levels of threat, adversity, support and nurturance that the growing child is likely to encounter and calibrating stress responsive biological systems to optimize survival, health and

developmental well-being (Ellis, Jackson, & Boyce, 2006; Ellis, Boyce, Belsky, Bakermans-Kranenburg, & van Ijzendoorn, 2011).

For example, Bakermans-Kranenberg and colleagues (Bakermans-Kranenburg et al., 2008) found that children with the DRD4 7R allele (a polymorphism in the dopaminergic pathway that has been linked to ADHD and risk taking), whose parents participated in the intervention, experienced the largest decrease in externalizing problems. Children who were carriers of the 'risk' allele reduced their externalizing scores by 27% over the follow up period (as compared to the counterparts without the risk allele, who decreased by just 12% over the course of the follow-up period). The authors concluded that 'risk alleles' can also create possibilities within intervention contexts. If these findings continue to hold, it means that what we have traditionally thought of as vulnerability, may best be conceptualized as plasticity and enhanced responsiveness (see for example (Belsky, Bakermans-Kranenburg, & van Ijzendoorn, 2007; Belsky & Pluess, 2009; Boyce & Ellis, 2005; Ellis & Boyce, 2008; Ellis et al., 2005)). Along the same line, recent work based on ÉLDEQ also shows that early non-maternal (day)care protects at-risk children from developing aggressive behaviours (Côté et al., 2007; Côté et al., 2010), and provides them with increased academic readiness at school entry (Geoffroy et al., 2010).

Indeed, individual differences in the effects of exposure to ACE appear to be the norm. Simply put, experience affects individuals differently. As described by Hertzman and Boyce (Hertzman & Boyce, 2010), from early in life, approximately 15% of children are more highly biologically reactive to their immediate social context than others. Over the life course the effects of being a highly reactive individual on psychiatric and biomedical outcomes are bivalent, rather than univalent in character, in that they can be protective in some contexts and risk augmenting in other contexts. In other words, heightened stress reactivity may not simply reflect exaggerated arousal under challenge, but rather an increased biological sensitivity to context, regardless of the context. For example, it has been demonstrated in child-care populations that there is a curvilinear, U-shaped relation between early exposures to adversity and the development of stress-reactive profiles, with high reactivity phenotypes disproportionately emerging within both highly stressful, and highly protected, early social environments.

Another way through which genetic factors may relate to the environment is by increasing or decreasing the likelihood of exposure to ACE. This may occur in a variety of ways, including through the child's influence on the behaviour of their caregivers, siblings and peers. This, in turn, may then be causally involved in the outcome through initiating a negative developmental chain of events. Behavioural geneticists refer to this sort of process as an evocative gene-environment correlation, meaning that characteristics of the child (which are, in part, under genetic influence) elicit a response from the environment (Jaffee & Price, 2007; Plomin, DeFries, & Loehlin, 1977; Scarr & McCartney, 1983). For example, exposure to initial and persistent peer difficulties at school entry was associated with genetic vulnerabilities underlying behaviour problems in the child (Boivin et al., in press-b). In other words, children who are at genetic risk for externalizing (and self-regulation) problems may also evoke negative responses from peers and thus create a context likely to maintain and reinforce their externalizing problems.

This is quite in line with the view that individuals often serve as determinants of their own environmental exposures, which can evolve over time into transactional patterns that drive

causation (Hertzman & Boyce, 2010). As described by Hertzman and Boyce (2010), early experiences can produce small changes in trajectories that can become magnified as the individual develops. As a hypothetical example, attachment maybe under parental control, but failure of the environment to properly signal and set up the reactions of positive attachment, in the amygdala and other brain regions of the child, may mean that the child will be at risk of missing significant social cues. This, in turn, can make the child less easy for care-givers and peers to relate to, which, in turn, can lead to deterioration of the child's immediate social environment; making it more stressful (Boivin et al., 2005). This vicious cycle, in turn, can have significant consequences for his or her social, emotional, and cognitive development. The bottom line here is that child factors and factors that are external to the child tend to become developmentally intertwined. It is important to understand these dynamic processes as they may be responsible for an individual becoming progressively entrapped in deleterious developmental trajectories of increasing negative and multifaceted outcomes.

5. Summary and conclusions

The goal of this chapter was to summarize what has been learned about the contributions of early life experiences to mental health, substance use and criminal involvement from longitudinal studies that have followed children from early childhood into young adulthood. The gain in knowledge in the past 10-15 years is substantial, and can be summarized in the following set of points.

1. **While not completely deterministic, exposure to adversity in early childhood increases the odds of poor mental health and unhealthy behaviours in adolescence and adulthood**. Longitudinal research has established strong and robust linkages between childhood adversity (including maltreatment, harsh parenting, and economic hardship) and developmental health, including adult psychopathology, criminality, substance use and associated mental health problems. In some cases, a dose response relationship between the number of ACE experienced and later psychopathology has also been documented. Evidence that experiences such as maltreatment and growing up with a parent who suffers from depression and/or antisocial behaviour has an environmentally mediated influence on children's future lives is generally supported by this body of research that relies on a variety of designs (prospective longitudinal, retrospective, high-risk 'genetically informative', and preventive trials) and samples (e.g., populations-based high risk, court involved, etc.). The environmental role of early exposure to substance use/abuse with respect to developmental health, including addiction, is less clear. However, there is evidence pointing to early adolescence as a transition period sensitive to family-wide and child-specific environmental factors.

2. **Exposure to adversity can set children on a risky trajectory early in life—a period of time when they are primed to receive and respond to input from their social worlds—and increase the likelihood that they will continue to encounter new stressors.** Not only is exposure to adversity not randomly assigned, but it also tends to persist through various developmental processes, thus increasing the risk of health and adjustment problems over time. The rapid absorption of experiences from the social world makes childhood a time when negative (and positive) inputs are likely to have

long-term and cascading effects on children's social and emotional development. Individuals who experience adverse events early in childhood are at an increased risk for experiencing repeated and chronic stressors at future stages of development. Creative research designs are required to tease apart the role or early versus later adversity altering children's developmental trajectories.

3. **Early-onset and persistent antisocial behaviour represents the most costly and detrimental pathway for children and is closely linked to childhood experiences of adversity.** One of the most costly life outcomes for an individual and society is involvement in criminal offending (Heckman, 2006). As demonstrated throughout this chapter, a robust link between ACE and involvement in antisocial behaviour in childhood, adolescence and young adulthood was documented. Over two decades of research in developmental psychopathology has also converged on the finding that early-onset and persistent involvement in antisocial behaviour represents the most costly and detrimental pathway for children (Moffitt, 1993; Odgers et al., 2008; Tremblay, 2000). Over the last 15 years, children showing early signs of behaviour and antisocial problems have been intensively studied, and their developmental trajectories described. A relatively small subgroup of individuals characterized by high and persistent behaviour problems, such as aggression and hyperactivity, is systematically identified (Nagin & Tremblay, 1999). This life-course persistent pathway of antisocial behaviour is characterized by social, familial and neurodevelopmental risk with onset in early childhood. In other words, individual, family and social risk factors are hypothesized to interact and lead to a wide range of poor outcomes as a vulnerable child is constantly exposed to adversity and stressors within high-risk familial and social contexts. As a result, the prevention of early-onset and persistent aggressive and other antisocial behaviour has emerged as a top priority for researchers, clinicians and educators with many believing that the prevention of early onset antisocial behaviour provides a key window of opportunity for altering children's future developmental trajectories. However, as we move forward it is important to note that more than half of the children who demonstrate signs of early-onset antisocial behaviour do not go on to follow the life-course persistent pathway (Odgers et al., 2007). As such, careful screening for signs of early onset *and persistent* antisocial behaviour are required to make the best use of limited intervention resources.

4. **Individual differences in the effects of exposure to ACE appear to be the norm. These differences are conditioned by a combination of individual level factors and environmental factors**. Although predictive, exposure to early adversity is not deterministic. There is a tremendous amount of variability in responses to ACE and a 'one size fits all' approach is not sufficient to understand the pathways from early adversity to poor mental health outcomes. The effects of early adversity are moderated by a wide range of factors from individual level factors, such as genes, to community level processes, including collective efficacy and social support (Yonas et al., 2010). The pervasiveness of G x E interactions, that is, the conditional association between biological vulnerability and social vulnerability, in accounting for later adjustment seems the norm rather than the exception. However, the story is still in the making as there are areas of "terra incognita" in knowledge regarding how G x E interactions act together over development to progressively create individual differences in developmental health.

5. **Intervening early though intensive programs aimed at the child and its proximal environment may have long-term beneficial effects for 'at risk' children and society.** Although poverty and socioeconomic deprivation are important ACE, we still have much to learn about how poverty reduction strategies could help reduce the burden of poor mental health and unhealthy behaviours in adolescence and adulthood. As pointed out in this chapter, poverty and socioeconomic deprivation are consistently found to be risk factors, and community function (such as collective efficacy) seems to buffer the relations between socioeconomic factors and adverse outcomes. Yet, to date, this evidence has rarely been translated into effective interventions that improve mental health and reduce unhealthy behaviours in adolescence and adulthood—through, for example, poverty reduction strategies or other forms of social change aimed at families facing socioeconomic deprivation. This is certainly an area that deserves more research.

6. **Children believed to be the most 'at risk' may also be the most responsive to interventions designed to enrich early environments.** The majority of research linking early life experiences to later mental health problems has focused on children's reactions to adverse experiences. In particular, some of this research has documented how children vulnerable due to individual-level factors may experience the worst of both worlds, as they are also more likely to experience a wide range of adverse experiences within their homes and communities. This story, however, may be changing. There is growing evidence that children considered to be most 'reactive' may also benefit the most from exposure to enriched environments or interventions. More generally, children who are viewed as the most 'at-risk' based on individual and genetic-level factors may also be the most sensitive to positive input from the environment. Thus, as we consider individual differences in reactions to adverse experiences, it is important to keep in mind the possibility that differential risk could also signal a greater opportunity for intervention and change in the lives of children. This is an exciting possibility and an area were additional research is needed.

CHAPTER THREE: THE NEUROGENOMIC SCIENCE OF EARLY ADVERSITY AND HUMAN DEVELOPMENT

This chapter focuses upon the emerging biology that links early life adversities with disorders of mental health and diminished well-being in adulthood. As such, the chapter addresses questions surrounding how ACE may influence the destructive morbidities of addiction and psychiatric disease, how exposures to abuse, poverty and family dysfunction affect development of critical brain structures on which mental health depends, and in whom these childhood stressors give way to the varied, prevalent and troubling disorders of adult life. The chapter adopts, and is organized around a conceptual model, shown in the figure below, that broadly affirms a primary linkage between early developmental adversity and long-term differences in health, development and positive functioning. In genetics, these differences are known as phenotypes or phenotypic differences, i.e., the observable characteristics or traits of an individual. It is argued that adversity and developmental health are connected through gene-regulating mechanisms and through individual differences in the structural and functional development of specific brain (and peripheral nervous system) circuits or pathways (see text boxes, below).

Associations between early adversity and healthy or maladaptive phenotypes are also mediated (i.e., relayed or facilitated) and moderated (i.e., magnified or diminished) by interactions involving characteristics of parenting, other close social contexts (e.g., childcare, early school), and genetic variation (i.e., DNA sequence variation; see Textbox, below).[3] Section I concerns the biological processes underlying the primary, longitudinal connections between early adversity and differences in health and development. Section II reviews current research findings on the role of G x E interaction and epigenetic processes in amplifying or diminishing the long-term implications of exposures to early stressors and adversities. Section I thus addresses primarily the mechanisms (i.e., mediators) linking adversity and healthy development, while Section II is concerned principally with the genomic moderation of those links. Chapter 4, which follows, then examines evidence that the adversity-phenotype differences association is altered in strength by aspects of parenting and close social contexts.

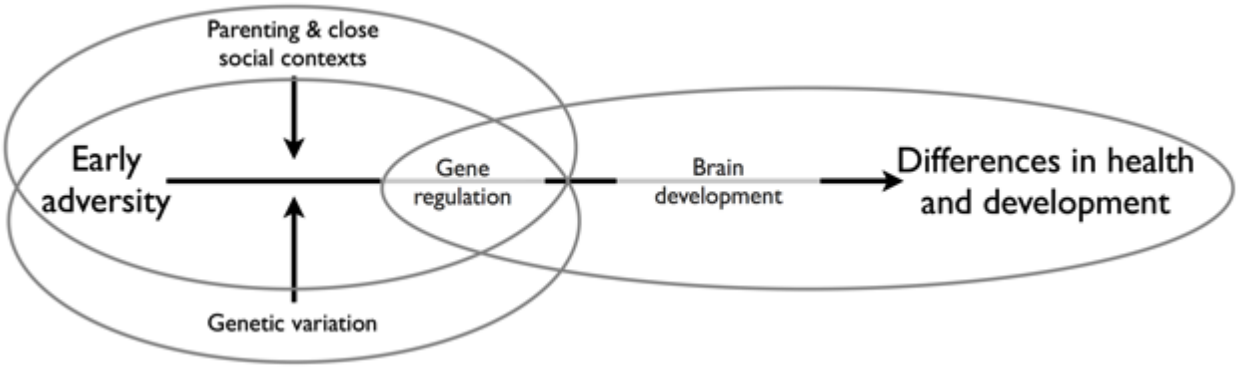


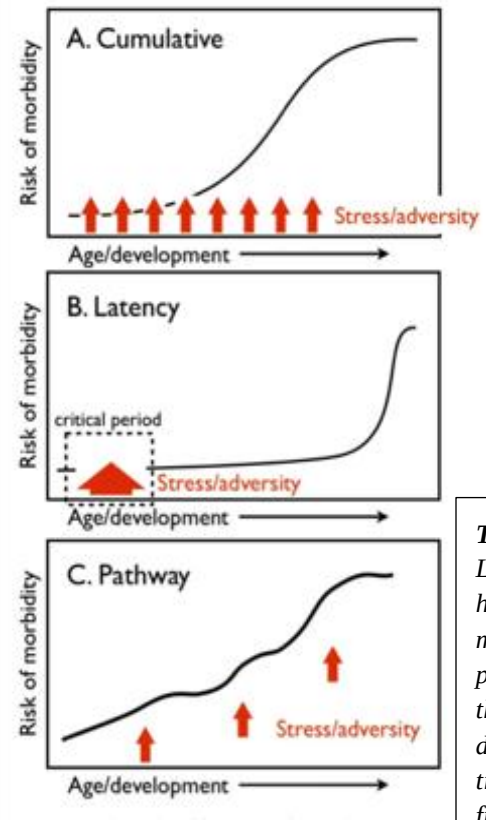
Figure 3.1. *Conceptual Model for the Neurogenomic Science of Early Adversity and Human Development*

[3] In keeping with the work of Baron and Kenny (Baron & Kenny, 1986) and Kraemer et al (Kraemer, Stice, Kazdin, Offord, & Kupfer, 2001), 'mediator' refers to processes that explain *how* or *why* an association occurs, and 'moderator' refers to factors that identify *when* or *in whom* an association holds.

1. Early adversity and variably adaptive phenotypes

Three convergent models describe early developmental and experiential influences on adult health (Hertzman & Power, 2003; Keating & Hertzman, 1999). First, such influences can occur through cumulative, differential lifetime exposures to damaging social and physical conditions (See Text Box 3.1). In a *cumulative* model, chronic diseases are viewed as the eventual products of long-term, progressive and repeated encounters with psychosocial or material environmental insults. Second, chronic disease processes can emerge through the effects of biological 'programming' during critical periods in early development. Critical periods are developmental intervals during which biological systems are especially sensitive or responsive to particular forms of environmental exposure or experience. In this second, *latency* model, adult diseases are seen as the end-results of critical environmental events that become embedded or implanted within neurobiological processes. Third, adult ill health can be the product of sequential escalations in risk, along pathways of periodic adverse childhood events. In such *pathway* models, early life environments set individuals onto life trajectories or tracks, which in turn affect health status over time. Although they distinguish three separate processes linking early experience with later health disorders, these models of early influence are not mutually exclusive. It is imaginable, for example, that coronary heart disease could be the product of both chronic, repeated exposures to socially partitioned (or socioeconomically dissimilar) childhood adversities, as well as nutritional deprivation during a single, critical period in fetal development.

2. Stress, health and development



Questions regarding the magnitude, character and mechanisms of these possible childhood influences on adult mental and physical health have been addressed in a steadily growing, though still incomplete, body of research from a variety of disciplines, including: social and life course epidemiology, population health sciences, demography, developmental psychology and developmental neuroscience. This multidisciplinary landscape of work has generated several converging lines of evidence that illuminate the long-term effects of childhood adversities on life course health and disease. As reviewed in the preceding chapter, a variety of both retrospective and prospective studies have identified

Textbox 3.1. Life course model of health outcome
Longitudinal effects of early stress and adversity on risk for adult ill health are thought to include cumulative, latency, and pathway models. Cumulative effects reflect the long-term 'wear and tear' of persistent or recurrent childhood adversities. Latent effects reveal the delayed risk of sustained stressors during critical periods of development. Pathway effects reveal changes in risk trajectory over time due to sequences of punctate adverse childhood events. Adapted from (Keating & Hertzman, 1999).

linkages between early childhood experiences of adversity and mental and physical health disturbances in later adulthood.

Other work has linked child maltreatment to long-term and potentially disease-associated alterations in hormonal and immune functions, and studies of institutionalized children in Romania and elsewhere have reported persistent aberrations in brain function and difficulties with the establishment of interpersonal bonds and relationships (Gunnar, Morison, Chisholm, & Schuder, 2001; Nelson et al., 2007; Rutter, Sonuga-Barke, & Castle, 2010). Together, these studies signal important, reliable linkages between stressors in childhood and the incidence and/or severity of a variety of chronic adult morbidities.

3. Adaptive developmental plasticity

While studies of ACE invoke a cumulative model of life course effects on health, another body of epidemiologic literature, amassed over the past twenty years, makes a quite different claim: that adult disease and disease risk factors are biologically programmed during critical periods of early growth and development, and remain latent until the emergence of pathogenic processes in adult life. Within this line of research, Barker and colleagues, at the Developmental Origins of Health and Disease program of the University of South Hampton, have produced a large body of findings indicating that chronic, life-threatening cardiovascular disease in mid- to late-life are derivative of nutritional deficits and impaired growth occurring in very early, even prenatal life (Barker, 1990; Barker, Osmond, Forsen, Kajantie, & Eriksson, 2005; Barker, 1997; Bateson et al., 2004; Eriksson, Forsen, Tuomilehto, Osmond, & Barker, 2001). In a series of retrospective cohort studies, they observed that individuals with low birth weight are at increased risk for coronary heart disease, even after statistically taking into account the influences of SES, age, race and sex. Further research, both prospective and retrospective, has identified reliable associations between low birth weight and a broad range of cardiovascular risk factors, including hypertension, central body fat distribution, insulin resistance, metabolic syndrome and type 2 diabetes mellitus (e.g., (Evensen et al., 2009) and (Fabricius-Bjerre et al., 2011)). Other work has suggested that pre- and post-natal growth deficiencies may both be independently linked to coronary disease risk (Barker et al., 2005). Based on these and other findings, developmental events during the earliest stages of human developmental are posited as pathogenic exposures that can influence the incidence of cardiovascular disease, psychiatric disorders, diabetes and respiratory disease.

Some reproductive epidemiologists have questioned the legitimacy of birth weight as an indicator of population health (e.g., (Wilcox, 2001)), and others point out that none of the Barker studies actually provided nutritional data, but rather use birth weight as a surrogate measure of nutritional well-being during gestation. Still others have decried the failure of epidemiologic investigators to design studies that are capable of falsifying the fetal origins hypothesis, with controls for potential confounding variables such as birth SES, diet, physical activity and smoking (Kramer, 2000). Although these studies have used historical information on birth weight that are not highly subject to bias, criticism has also focused on the possibility of statistical artifacts in the analysis of data and the suggestion that any causal effect of fetal under-nutrition on adult morbidities is likely to be small in magnitude, relative to the traditional, known risk factors for chronic disease.

On the other hand, the hypothesis and findings of Barker and colleagues are commensurate with evidence from other animal and human research. Four decades ago, researchers showed that nutritional deficits in rat pups over the first three weeks of life permanently diminished their capacity for weight gain over the remainder of the lifespan, even when high quality food was made available (Widdowson & McCance, 1963). Dubos invoked 'biological Freudianism' to highlight the enduring biological effects of early environmental perturbations in laboratory animal experiments (Dubos, Savage, & Schaedler, 1966). In more recent work, low birth weight due to fetal growth restriction in rats, induced by shutting down blood supply to the uterus, was associated with higher baseline and stress-reactive blood pressure (Schreuder, Fodor, van Wijk, & Delemarre-van de Waal, 2006), and studies of human infants have linked prenatal growth restriction to control of the heart by the autonomic nervous system (Massin, Withofs, Maeyns, & Ravet, 2001) and to high blood pressure at six years of age (Shankaran et al., 2006). So-called "natural experiments", in which groups of human infants have been subjected to transient nutritional deficits due to historical events, have also offered corroborating support. Dutch famine data, for example, have found that exposures to famine in the first trimester of pregnancy are associated with increased risk of coronary disease in offspring (Roseboom et al., 2000).

The fetal origins work is also consistent with known mechanisms by which early environmental signals influence the adjustment of important biological systems. 'Conditional adaptations' are evolved biological mechanisms that monitor early environments—including the prenatal environment—as a basis for calibrating the development of important brain structures and circuits (Belsky, Steinberg, & Draper, 1991; Boyce & Ellis, 2005; Ellis, 2004). Such adaptations produce phenotypic versatility, in which a single, individual genome is capable of producing a broad range of physical or functional traits. Fetal responses to prenatal nutritional signals, for example, could plausibly allow the fetus to adjust postnatal metabolic 'expectations' appropriate to the anticipated conditions. Thus, fetuses developing in prenatal environments characterized by under-nutrition, and therefore sustaining impaired growth and low birth weight, might undergo adaptive, energy-sparing metabolic changes. The problem arises when the adaptive 'prediction' of postnatal life is wrong, and the period of prenatal energy deficits are followed by a postnatal life of energy abundance, a carbohydrate-rich diet, and a sedentary life style (Worthman & Kuzara, 2005). Under these conditions, an infant with low birth weight who grows up in an affluent, food-rich environment could have an increased risk of coronary heart disease, type 2 diabetes and hypertension (Gluckman & Hanson, 2004). The combination of prenatal nutritional deprivation, followed by accelerated postnatal growth—that is, a mismatch in terms of evolutionary adaptation (Gluckman, Hanson, & Beedle, 2007)—might thus form the basis for a contemporary, epidemic cause of premature mortality.

4. The biological plausibility of adversity-phenotype associations

While the evidence for long-term linkages between childhood events and adult health has been steadily growing, evidence of its biological plausibility has also dramatically increased over the past 10-15 years. Converging findings now show that psychosocial stressors are capable of augmenting liabilities to disease through neural and genomic pathways. Extensive work by an array of investigators (Chrousos, 1998; Gunnar, Wewerka, Frenn, Long, & Griggs, 2009; Heim, Ehlert, & Hellhammer, 2000; Heim, Newport, Mletzko, Miller, & Nemeroff, 2008; McEwen, 1998; Sapolsky, 1996; Sapolsky, Romero, & Munck, 2000) has mapped the brain circuits and

peripheral neuroendocrine pathways through which experiences of adversity are changed into biological processes leading to disease and disorder. Other research, in both animal and human models and using both molecular and developmental-epidemiologic methods, has revealed previously undiscovered processes by which variation in DNA can interact with environmental exposures to change disease risk (Caspi et al., 2002; Caspi et al., 2003; Rutter, 2007; Rutter, Moffitt, & Caspi, 2006) and by which variation in social contexts can affect the expression of key regulatory genes (Szyf, McGowan, & Meaney, 2008; Weaver et al., 2004). It is to these new sciences—of stress neurobiology and gene-environment interplay—that we now turn.

a. Stress neurobiology

i. Neurobiological transduction of adversity

Among the thematic findings of the new neuroscience of stress and adversity is the delineation of the role of brain circuits underpinning short-term memory (the hippocampus), the detection and appraisal of threat (the amygdala), emotion regulation and executive functions (the prefrontal and anterior cingulate cortex (PFC and ACC)) (Cacioppo, Tassinary, & Berntson, 2000). These structures and their inter-connecting circuits are organized into the two branches (sympathetic and parasympathetic) of the autonomic nervous system (ANS), which play counter-balancing roles in stress reactivity, and the hypothalamic-pituitary-adrenocortical (HPA) axis, which also exerts powerful regulatory influences on the ANS and the overall stress response (Sapolsky et al., 2000). Acting in concert but within differing response timeframes, these systems help control a variety of peripheral, target tissues, including immune cells, the heart and circulatory system, the endocrine processes managing blood sugar and other metabolic processes, and the dynamics of gastrointestinal function. The ANS and HPA systems are correspondingly activated by a small cluster of neurons in the brainstem (the locus coeruleus) and an assembly of structures at the center of the brain (the hypothalamus and anterior pituitary) that collectively produce corticotropin releasing hormone (CRH) and adrenocorticotropic hormone (ACTH), the substances triggering secretion of the stress hormone, cortisol. Together, these systems process incoming information from the external world, assess the emotional content of such information, and generate calibrated neurobiological and behavioural responses intended to return the organism to balance and control (or homeostasis) (Cacioppo, 1994; Cacioppo, Berntson, Sheridan, & McClintock, 2000; Chrousos, 1998; Gold & Chrousos, 2002). There is substantial evidence that these stress-responsive systems are highly pliable in the young and are extensively shaped by early experiences of stress and parental care (Levine, 1994; Meaney, 2001; Suomi, 1999). Although the *sine qua non* of the stress response has been an elevation of blood and salivary cortisol levels, growing evidence indicates that, under conditions of chronic, unrelenting stress (such as a child might experience in an orphanage or in other institutional care), a persistent lowering or down-regulation of cortisol expression can develop, consisting of a decrement in early morning levels and diminished ACTH and cortisol responses to stressors (Loman & Gunnar, 2010).

Collectively, the brain and peripheral stress response systems act in a coordinated manner to guide and maintain a dynamic regulatory process known as allostasis, or the attainment of physiological stability through biological or behavioural change. Allostatic load—i.e., the regulatory wear-and-tear constituting the biological cost of homeostatic control—accumulates

over time among children sustaining chronic or recurrent adverse events. These recurrent events lead to exaggerated, maladaptive physiologic responses, escalate disease risk, and undermine health both in childhood and in adult life (Karlamangla, Singer, McEwen, Rowe, & Seeman, 2002; McEwen & Gianaros, 2010). Maladaptive responses might include, for example, stress-related impairments in immune function (Ader, Felten, & Cohen, 2001; Boyce et al., 1993; Cohen et al., 1997; Cohen & Williamson, 1991; Sheridan, Stark, Avitsur, & Padgett, 2000), acceleration in rates of infectious and chronic diseases (Cohen, Janicki-Deverts, Chen, & Matthews, 2010; Cohen, Miller, & Rabin, 2001; Cohen, Tyrrell, & Smith, 1991), or increases in blood pressure and cardiovascular disease incidence.

The brain and involved brain structures serve not only as points of origin within these coordinated stress responses, but also as targets of feedback from physiological processes in the periphery. The hippocampus, as one example, is among the most sensitive and modifiable brain regions and can be both functionally and anatomically restructured by signaling associated with peripheral neural processes (McEwen & Gianaros, 2010). Hormones and medications, such as estradiol and antidepressants, exert important influences on the replacement of neurons, and the cortisol response to chronic stressors can alter micro-anatomical features of hippocampal neurons, such as the number and complexity of connections with other cells. Together, these processes can alter both memory and the stress response control functions of the hippocampus. The prospect that peripheral signaling pathways can alter key brain structures is also supported by evidence that experimental manipulation of relative social standing is capable of changing amygdala reactivity (Zink et al., 2008) and that low social standing is associated with decrements in gray matter (the major portion of the cerebral cortex containing neuron cell bodies) in the anterior cingulate cortex (Gianaros et al., 2007). Both of these observations suggest that social experience, especially experiences of differential social status, can produce measurable change in the function and structure of specific brain regions. It is to these experiences, especially the multifaceted adverse conditions associated with low SES, that we now turn.

ii. Brain development and adversity associated with low socioeconomic status

Socioeconomic inequalities in both experiences of sustained adversity and disorders of mental and physical health, described in the Introduction, have also been rendered more biologically plausible by a new vanguard of studies examining systematic differences in brain development among children reared in families of disparate SES or in environments of abuse, deprivation or adversity. Importantly, these studies reveal neurodevelopmental differences across the entire spectrum of SES, not just at the impoverished end, suggesting that these neural differences linked to social position apply to the entire population, albeit to different degrees (Hackman et al., 2010). Among studies examining socioeconomic disparities in neurocognitive functions, the largest differences have been found in language processing and executive function, presumably related, at least in part, to the considerable differences between low and high SES families in the volume and complexity of parent-child verbal communication (Forget-Dubois et al., 2009; Hart & Risley, 1995). Several studies have reported differences in the response characteristics of the prefrontal cortex (PFC) in electroencephalographic (EEG) and fMRI studies between children from lower and upper SES families (D'Angiulli, Herdman, Stapells, & Hertzman, 2008; Farah et al., 2006; Hackman & Farah, 2009; Kishiyama et al., 2009; Sheridan, Sarsour, Jutte, D'Esposito, & Boyce, 2012). Together, these studies suggest that low SES children tended to have deficits in

selective attention, to be less able to filter distractions, and to fail to recruit the PFC in the detection of novel stimuli. Such prefrontal deficits appear to extend to emotion regulatory functions, as well, with lower SES youth showing prefrontal differences in cortical activation, commensurate with those seen in patients with major depression (Tomarken, Dichter, Garber, & Simien, 2004). Within animal models, these differences in PFC functional pathways, as well as structural changes, have been shown to occur as a result of the activation of stress response systems early in life (Holmes & Wellman, 2009).

iii. Neurobiological 'costs' of early adversity

Disadvantaged children's heightened neurobiological sensitivity to aversive social contexts can thus be seen within stress-responsive neural pathways, such as the ANS and HPA axis (Boyce et al., 2010; Evans & Kim, 2007; Lupien, King, Meaney, & McEwen, 2000; Steptoe & Marmot, 2002). The differences in brain circuits that emerge among children from different socioeconomic groups have the capacity to exert profound influences on developmental health, cognitive function, and educational attainment. These differences in stress reactivity may also be trans-generational in character, as animal models indicate that prenatal administration of glucocorticoids (such as cortisol or corticosterone) to pregnant females, simulating responses to the adversity sustained by low SES mothers, results in delayed formation of the myelin sheath around neurons, decreased production of inter-neuronal connections, and inhibited generation of new neurons in the fetal brain (Hackman et al., 2010). There is further evidence that the exaggerated reactivity of young rats can be transmitted to a second and third generation through *epigenetic mechanisms* (see Textbox 3.2 for definition) triggered by maternal care (Meaney, 2010; Meaney & Szyf, 2005; Szyf et al., 2008; Weaver et al., 2004).

Considered together, these observations signal convincing epidemiological, clinical and neurobiological linkages between experiences of early childhood adversity and long-term risks to human development and health. The extent to which such associations reflect gene-environment interplay, and whether such associations adhere to cumulative, latency or pathways models of disease pathogenesis is not clear. However, the evidence converges on a single, potent reality: that the biological repercussions of stressors and adversities sustained in early life continue to echo through the decades of adult life, systematically escalating rates of mental and biomedical disorders and the chances of early mortality. These associations are not, moreover, simply 'statistical' in character; rather, they are undergirded by a growing collection of human and animal studies documenting the neurobiological plausibility of stress-illness associations. Significant exposures to adversity, especially those sustained in early childhood and within family environments of poverty and deprivation, are capable of altering the structure and function of brain circuitry and the reactivity of peripheral stress responsive pathways, and these changes comprise the biological foundation for lifelong escalations in mental and physical disorder. What remains to be elucidated are the actual molecular biological processes by which experiences and biology act together to produce differences in health, a set of processes to which we now turn.

b. Gene - environment interplay

i. Genes and the environment

In the previous chapter, we have discussed the question of gene-environment interplay as it relates to the prediction of individual differences in developmental pathways. Here we provide more information on the biological foundation of these processes.

According to Wahlsten and Gottlieb (Wahlsten & Gottlieb, 1997), "Environment regulates the actions of genes, and genes, via changes in the nervous system, influence the sensitivity of an organism to changes in the environment. The two causes are not separable developmentally (within an organism), yet, this can be analyzed at the level of individual differences. As development progresses there is a constant interchange between genes and environment. Investigating the interdependencies between genes and the environment is critical for developing a deep understanding of both the proximate and ultimate contributions to individual differences.

We now understand from recent advances in molecular biology and genomics that DNA (*Deoxyribonucleic acid*, a molecule containing the basic genetic information, i.e., the genes) is not only inherited but also environmentally responsive, as if our genes were listening to the environment. By environmentally responsive we mean that the ability of the DNA to make its RNA (Ribonucleic acid, a molecule acting as an intermediary in protein synthesis and thus controlling gene expression) and protein gene products (i.e., the gene expression) changes depending on the environment. In other words, gene expression can be turned on, turned off, or increased or decreased depending on input from the environment. These variations in gene expression add a layer of complexity to an already multifaceted picture of gene-environment interplay in development. We learned that individuals who differ in the DNA sequence of a gene may be differentially affected by the same environment (see discussion of Caspi and Moffit's work in the previous chapter). However, not only does an environment affect individuals across development as a function of their genetic variant (DNA sequence), but also, as briefly illustrated in the previous chapter, individuals, by virtue of their genetic variants, may also select or evoke certain environments. In turn, their experiences in a chosen or evoked environment can also affect the expression of their genes. Finally, individuals sharing the same genetic variants may see their genetic makeup differentially modified by experience (epigenetics) and this modification may be inherited.

G x E interdependencies are thus extremely complex, and their studies, tremendously challenging. The environmental input is necessarily multifaceted and laced with physical and biological factors that vary in time and space. From conception onwards, environments act like dimmer switches dialing gene expression up or down. However intricate these processes are, their study at the mechanistic level is now possible and timely, given the new tools in genetics, molecular biology, genomics and brain and body imaging that greatly facilitates these studies. Gene-environment interplay is now further discussed from the perspectives of gene by environment interactions and epigenetics.

ii. Gene by Environment (G x E) interactions

Gene by environment (G x E) interactions are now commonly found in both animal and human studies ((Rutter, 2007); see previous chapter on longitudinal studies). Here we use the term 'genetic' to denote variation in the DNA sequence of a gene. Briefly, a single gene is a long stretch of DNA that may vary across individuals in its sequence of nucleotide bases (e.g., ATCGGG versus ATCGCG). This difference in DNA sequence can have consequences for the RNA that gets transcribed from the gene's DNA and the protein that gets translated from the RNA. DNA variations, also loosely called genetic polymorphisms, may be in 'coding regions', whose information is used to make the protein, or in 'regulatory regions', which indicate where in the organism, and when during development, the protein should get expressed. Thus, individuals differing in a DNA variant within a single gene can differ in the type of protein made by the gene (genetic polymorphism in the coding region), or in the regulation of the gene (polymorphism in the regulatory region of the gene). These DNA variations contribute to individual differences. Genetic polymorphisms can also affect whether and how the gene responds to an environmental signal (Sokolowski & Wahlsten, 2001).

However, in examining this question (i.e., the genetic contribution to behavioural variation), it is important to underline that genes do not determine, control or cause behaviour in the strict sense of those words. 'Genetic determinism' implies a direct and necessary association between a gene and a given phenotype (physical or behavioural trait). According to this rather basic and overly simplistic model, when the 'allele' (i.e., a particular DNA variant of a gene) for a behavioural trait is present, the organism will always exhibit the trait. Unfortunately, this sort of deterministic thinking ignores the role of the environment in behavioural variation, as well as possible G x E interactions (not counting gene by gene interactions). We now know that, rather than determining behavioural traits all on their own, genes actually influence a probability that behavioural traits will be expressed in a given environment. Genetic determinism rarely, if ever, applies to complex behavioural traits in individuals or in populations. This is true when a single DNA polymorphism affects a behavioural trait (discussed in the previous chapter) and in the more common cases when many genes (polygenic inheritance) influence, often in interactive ways, individual differences in behaviour.

In human populations multiple genes interact with multiple environments over developmental time, which makes investigations of these processes quite a challenging task. Fortunately, animal (i.e., non-human) models allow dissection of these many factor interactions for investigations of causation.

There is another common misunderstanding concerning the role of genetic factors in development; that stemming from the confusion between trait inheritance, i.e., the degree of genetic influence on a trait, and trait plasticity, i.e., the extent to which it can be modified by the environment (Sokolowski & Wahlsten, 2001). The misconception is that when a trait is "more genetic" it will necessarily have a narrower range of responses to changes in the environment, whereas when a trait is "less genetic" (and more associated with environmental variation), behavioural variation has a greater range of phenotypic possibilities. In other words, environmental influences are thought to cause greater variability than genetic ones. This inaccurate view ignores two important facts. First, the derived estimates genetic and

environmental contributions to a given trait refer to how things are or have unfolded, and not as they could be if there was a change in the environment. Second, the model underlying this position is one where the genetic contribution and the environmental contribution to trait differences are ADDED. Significant findings of G x E interactions are ignored in this view. This misguided view is found in some of the human literature with regard to traits such as IQ, sexual orientation and psychiatric disorders (Sokolowski & Wahlsten, 2001).

In the past ten years, G x E interactions have typically been studied from the perspective of allelic variation in a single gene. Candidate genes are chosen based on their known function in animal models and human studies (Fitzpatrick et al., 2005). For example, candidate genes in the stress response pathway have been used to investigate resilience and vulnerability as G x E interactions with respect to early adversity (Feder, Nestler, & Charney, 2009). This candidate gene approach is possible because we know about (1) the range of normal individual differences in stress responses and related neurocognitive development, (2) the inherited variation for these individual differences, and (3) the specific genes that play a role in stress and neurocognitive development. But again, there is a long list of possible intervening mediators accounting for the stress response. Indeed, many pathways, hormones, neurotransmitters and neuropeptides play a role in physiological and psychobiological responses to stress: the hypothalamic-pituitary-adrenal (HPA) axis, the neuroadrenergic, serotonergic, dopamine systems, as well as other influences such as neuropeptide Y and brain-derived neurotrophic factor (BDNF) are involved in the function and regulation of responses to stress. Accordingly, each of these components may affect individual differences in stress responses.

There is a complexity of interactions between a child's genetics and his or her exposure to environmental adversities or enrichments during development that affect the adaptation of the stress response system and the development and functioning of the neural circuitry involved in stress responses. Because the human genome has been fully sequenced, databases of human genetic (DNA) variants are now available for most genes, including those involved in the stress response system. Abundant genetic variation in genes that affect these stress responses are known, and these genetic variants interact with early adversity to affect the physical and behavioural traits during development and have consequences for adult health, learning and functioning in society (Feder et al., 2009). The timing and type of early adversity during development also interacts with genetic variation to affect physical and behavioural outcomes.

There are many documented examples of G x E interaction. For example, genetic variation in the CRH receptor gene (CRH1) moderates the effects of child abuse on adult depression; certain alleles of this gene provide protective effects from early adversity (Bradley et al., 2008). One of two allelic variants of glucocorticoid receptor gene (GR) results in greater cortisol responses to the Trier Social Stress Test, a stress inducing public speaking and mental math task (DeRijk & de Kloet, 2005). As indicated in the preceding chapter, one of the best examples of G x E interaction involves allelic variation in the serotonin transporter gene (5-HTTLPR) and its interaction with early experience (Caspi et al., 2003). 5-HTTLPR encodes for a protein involved in serotonin reuptake. As described earlier, studies of this gene in nonhuman primates and in human populations have discovered a promoter linked polymorphic region that interacts with early experience to effect behaviours in young and in adults (Murphy & Lesch, 2008). The long and short alleles result from a 43 base pair (see description of DNA above) insertion/deletion in the

promoter region of the 5-HTTLPR gene. In humans, the short allele leads to approximately three times reduced transcription of 5-HTTLPR mRNA compared to the long allele under 'basal' conditions in the laboratory (Heils et al., 1996), and this 43 base pair difference could make a difference in the lives of those affected by this short version of 5-HTTLPR gene. Indeed, these allelic variants were differently associated with depression and other related behaviours when an individual had a history of adversity early in life (Caspi et al., 2003). In general the short allele is thought to confer risk to early adversity while the long allele confers protection. However this is not always the case. For instance, Mileva-Seitz, et al (Mileva-Seitz et al., 2011) showed that only the long allele of the serotonin transporter gene negatively affected maternal sensitivity to six-month-old infants when there was a history of abuse.

Another example of G x E interaction involves the brain-derived neurotropic factor (BDNF), a small protein (known as a peptide) that supports neural growth and survival (reviewed in (Casey et al., 2009)). There is a common genetic variant in BDNF that is found in 20-30% of humans. Individuals with this variant of the gene have impairments in activity-dependent release of BDNF. That is, when exposed to early adversity these individuals show impairments in certain forms of learning and memory and are more susceptible to psychiatric disorders. *The key point of these findings and those presented earlier is that allelic variation in a single gene can differentially affect a child's susceptibility to early adversity*, making some children vulnerable and others seemingly protected from the environmental exposure.

However, these G x E interactions have more than one level of complexity as they can change throughout development as well as in different tissues of the body. For instance, the protective effects of an allele at one stage may not extend to all stages of development. In addition, BDNF expression changes throughout development, but in different ways in different brain regions. Accordingly, researchers think that the effect of the genetic variant changes from phase to phase as the child grows up, according to the changing need for BDNF in different regions of the brain (Casey et al., 2009).

iii. The future of G x E interaction investigation

Genome Wide Association (GWAS) studies now allow us to correlate the variation in a trait or a disorder with all possible variations in the genome (hence Genome Wide). This approach is increasingly used to investigate 'risk alleles' for psychiatric disorders (Beardslee, Chien, & Bell, 2011), and this type of research will soon consider early exposures to environmental adversity to broaden GWAS within a G x E interaction framework. This relatively new approach will likely identify novel genes and pathways involved with the trait of interest and allow researchers to understand how risk associates with early experience. GWAS commonly uses upwards of 500,000 DNA differences to identify genetic variants that associate with particular traits. Soon the cost for genome wide sequencing will make GWAS a better choice than studying genetic variation one gene at a time. Integrating the G x E approach into genome wide analyses will (1) increase the number of risk alleles identified, (2) relate these alleles to early adverse exposures and (3) investigate how the relative importance of each G x E changes through development and during adulthood.

Genome wide approaches are also used to study the RNA levels of all of the genes expressed in a given tissue. This 'transcriptomics' approach is performed using microarray analyses and more recently RNA sequencing (Gibson & Muse, 2009; Kent, Daskalchuk, Cook, Sokolowski, & Greenspan, 2009). In microarray analyses, the expression level of each gene is measured in a specific tissue and compared between individuals that differ in environmental exposures. In RNA sequencing, all RNA species within the tissue of interest are sequenced for individuals who experienced different environments. This genome wide approach has been used primarily in animal research. One exception (Duric et al., 2010) used RNA expression profiling of postmortem hippocampal tissue of subjects with major depressive disorder compared to matched controls. They identified an important regulator of the 'MAPK cascade,' (i.e., a key metabolic pathway regulating responses within cells to external stimuli) involved in neuronal plasticity, function, and survival as a key factor in major depressive disorder. Further experiments confirmed a causative role for this gene in mouse models of depression. Studying all the genes in an individual at the same time (genome wide approaches) will soon provide the means to reach the next step in assessing G x E interactions.

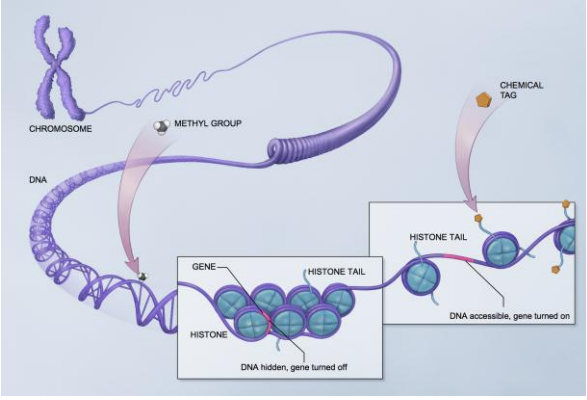
iv. G x E and sensitive periods

Early development is a time when interactions between the environment and genotype are seen as particularly sensitive, even critical for later health and behavioural outcomes. The timing of environmental input may be critical for the development and performance of later behaviour, even for normal behavioural development. A "critical or sensitive period" is a time when a developing organism shows a heightened sensitivity to particular environmental stimuli, such that the organism's later development is significantly altered due to its experiences during this period. Here, we use the term sensitive, rather than critical, to indicate that, in humans, the periods of concern tend to be more prolonged and have less sharply demarcated boundaries of influence, than in many other animal species. The basic idea behind the sensitive period hypothesis is that in the absence of appropriate stimulation during a particular sensitive period, the development of the putative competence, behaviour, or health outcome, may be compromised (Hensch, 2005).

There are good reasons to think, and reasonable means to test whether G x E interactions are more likely to play a significant role during sensitive period, but this has not yet been tested systematically among humans (Takahashi, Takahashi, & Liu, 2010). However, there is indirect evidence that it may be the case (see Ouellet-Morin et al, discussed in the previous chapter) (Ouellet-Morin et al., 2008; Ouellet-Morin et al., 2009). Furthermore, research on rhesus monkeys shows persuasive evidence for specific G x E interactions framed by a sensitive period in development. When monkeys were reared in infancy with peers rather than with mothers, the short allele polymorphism in the promoter region of the serotonin transporter gene has been associated with poor neuronal function in infancy and poor control of aggression in the juvenile and adolescent periods. In contrast, monkeys with the short allele, raised during this period of development with peers and their mothers did not exhibit these deficiencies. Finally, monkeys with the long allele are normal for all of these factors regardless of their early social rearing (Suomi, 2006).

Thus, the importance of developmental periods, of maternal and other social input, and of certain sensory stimuli during critical periods of development, often through complex G x E interactions, is well established for a variety of animals, including insects, rodents, and primates. It is thus unfortunate and quite misleading that the language of 'nature-nurture' dichotomies predominates. The ease with which we slip into this faulty language may be partly due to the powerful influence of parental nurturing that is thought to be so important for human development. It is therefore noteworthy that recent developments in the study of epigenetics suggest that that epigenetic inheritance may be involved in parenting. This will be addressed in the next chapter.

5. Epigenetic changes as an interface between nature and nurture



(National Human Genome Research Institute)

Textbox 3.2. Epigenetics defined

Epigenetic' means literally "upon genes." The term refers to chemical processes and modifications that change the structure, conformation or packaging of DNA, which in turn facilitate or disallow the transcription (decoding), and expression, of the gene. As shown in the figure above, the chromatin—consisting of the DNA strand wound around histone proteins, like beads on a string—can be altered by a variety of chemical 'marks' or tags, which include DNA methylation and histone modification. Such marks trigger the loosening or tightening of the chromatin structure and thus determine the accessibility of the gene to the molecular machinery that facilitates the decoding of the gene by the enzyme RNA polymerase.

In contrast to epigenetic differences, "allelic variation" or 'gene polymorphisms' refer to variability in the chemical DNA sequence itself of a given gene. This variability can occur either in the part of the gene that encodes the structure of its protein product (i.e., the exon) or the part that determines when and how much protein is made (i.e., the promoter region).

a. Epigenetic transduction of adversity

A new level of complexity in the evaluation of inheritance has appeared within the last decade. Epigenetics (see Textbox 3.2) introduces another layer of biological substrate into the relationship between phenotype and genes. Epigenetics is the study of changes in gene expression that occur through mechanisms that don't involve changes in DNA sequence. Examples of these are DNA methylation and histone modification. In DNA methylation, methyl groups are added to the DNA. Highly methylated areas of DNA tend to make less RNA because they are less active in the process of transcription; causing a halting or reduction of gene expression. In histone modification the chromatin that interacts with the DNA is modified resulting in a change in the amount of gene expression. Bird defines epigenetic events as "the structural adaptation of chromosomal regions so as to register, signal, or perpetuate altered activity states." (Bird, 2007). In this seminal review, he goes on to write that "…epigenetic processes are buffers of genetic variation, pending an epigenetic (or mutational) change of state that leads an identical combination of genes to produce a different developmental outcome" (p. 398). This definition bridges between developmental biology and behaviour and clearly declares that an epigenetic event is a response to the environment. In other words, this source of inheritance emphasizes the relationship between the environment and the phenotype. Epigenetics regulates gene expression (the amount of RNA

and then protein made by a gene) without altering the genotype (DNA sequence). This new understanding is especially important to this report because one of the best examples of an epigenetic process relates to a social behaviour especially relevant to our main question: the maternal influence on stress response.

We now take note of several examples of how epigenetics plays out in humans and animals, in ways that are relevant to the developmental health outcomes that are the focus of this report. Indeed, one key insight into how early adversity may get under the skin to affect well-being comes from the epigenetic regulation of the HPA axis. In mammals, the HPA axis is controlled in large measure through the expression of glucocorticoid receptors (GR) in the hippocampus, and through its feedback in the hypothalamus, two important brain regions. Increased production of GR typically results in greater negative feedback on the secretion of CRF (from the paraventricular nucleus of the hypothalamus) and ACTH (from the anterior pituitary), resulting in diminished cortisol responses to aversive stimuli. Work on the rodent model done by Meaney, Szyf and colleagues (Meaney & Szyf, 2005; Szyf et al., 2008) documented that naturally occurring, or experience-related differences in maternal caregiving, in the form of licking and grooming of the newborn pups, affects the responsivity of the pups' HPA axis. This early calibration of a stressful environment is then set in place for the remainder of the lifespan.

Szyf, Meaney, and colleagues have characterized an epigenetic mechanism for determining stress responses in rats. In this 'maternal programming' (Szyf, Weaver, Champagne, Diorio, & Meaney, 2005; Weaver et al., 2004; Weaver et al., 2005), the response to stress is mediated by glucocorticoid receptors in the hippocampus, an area of the brain central to learning and memory. Levels of glucocorticoid receptors are affected by licking and grooming provided by mothers during the first week of life. Offspring of mothers that lick and groom at high levels produce more copies of the glucocorticoid receptor mRNA, while offspring that receive less licking and grooming make fewer copies. In addition, the offspring of mothers with higher levels of licking and grooming are better able to cope with stress. In contrast, individuals that received higher maternal stimulation were less reactive to stressful stimuli based on a variety of behavioural, neural and neuroendocrine measures (see Textbox 3.3 for a detailed mechanistic description of the process).

Two critical observations call attention to this work. First, the expression of the glucocorticoid receptor is influenced by patterns of DNA methylation (see Textbox 3.3) within the gene that encodes the receptor. DNA methylation is a type of epigenetic modification of the DNA that does not change the original DNA sequence. In this case, the part of the gene that tells it when to turn on and off (the promotor) of the glucocorticoid receptor is methylated (a methyl group is added) resulting in a decrease in the amount of RNA that this gene makes (decreased gene expression). The level of licking and grooming received by the pup establishes these patterns. The patterns are maintained into later stages of life and they can be manipulated to alter responses to stressful stimuli based on experience. Thus, the changes in gene activity in response to stress are controlled by patterns of methylation that define an epigenetic response to mothering. Second, the stress response-related effects of maternal licking and grooming are passed on to female offspring. The female offspring treat their offspring according to how they themselves were reared (with high or low licking and grooming).

Szyf and his colleagues (Weaver et al., 2005) found that the transmission of this maternal behaviour across generations is related to methylation of the estrogen receptor gene passed from mother to daughter. In a related human study (McGowan et al., 2009), it was shown that methylation patterns and RNA expression levels of the glucocorticoid receptor in the hippocampus of the brains of suicide victims were altered when the victims had a history of abuse. In humans, increased methylation of the Nr3c1 gene that encodes GRs has been associated with both a history of childhood abuse (McGowan et al., 2009) and with suicide (McGowan et al., 2008). Using pilot microarray analyses of gene expression within defined pathways, Nater and colleagues (Nater et al., 2009) identified multiple pathways in which gene expression was altered from baseline to immediately following a standardized, social evaluative stressor and between the stressor and a recovery period. Implicated biological pathways included cell cycle, cell signaling, adhesion and immune responses to the stressor. All this suggests that, as with low licking and grooming in mice, early adversity in humans results in changes in the expression of genes that help us cope with stress.

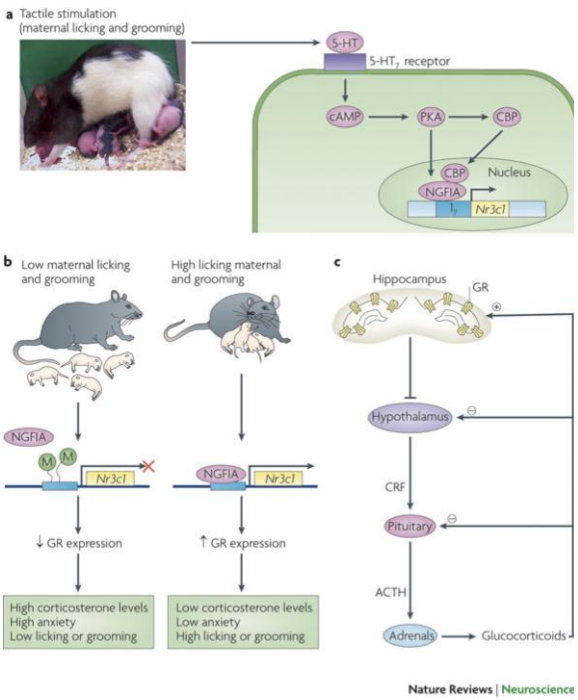
Other animal models have similarly revealed diverse pre- and postnatal exposures—including nutritional supplements, ionizing radiation, and environmental toxins—that are capable of epigenetically modifying the risk and/or severity of disease (Jirtle & Skinner, 2007). Epigenetic marks are transmissible across cell divisions (i.e., mitosis), but are substantially revised in the course of division of the egg and sperm cells (Relton & Smith, 2010). There is some evidence within animal models that environmental exposures can operate inter-generationally to affect the epigenome of offspring (Bollati & Baccarelli, 2010).

Epigenetic modifications are not, however, the only molecular mechanism by which environments influence the functioning of genes and the risks of maladaptive outcomes. In both young rhesus macaques (Kinnally et al., 2010) and human children (Meaney, 2011), sequence variations in the genes that establish serotonergic pathways in the brain have been shown to engage GxE interactions, leading to disorders of socio-emotional development.

Although there are not yet many examples of robust epigenetic effects on behaviour, the example of maternal behaviour in rats implies a level of complexity that is greater than G x E interactions. The inheritance of a phenotype must account for several tiers of plasticity both within the genome and ‘around’ it.

Meaney and Szyf’s pioneering discovery was that this conditional adaptation, by which infants’ neuroendocrine responses to stressors are matched to the level of environmental adversity, signaled by the mother’s caregiving behaviour, is mediated by epigenetic modifications that modulate expression of the GR gene (Weaver et al., 2004). In adulthood, pups receiving high maternal care also express more receptors for GABAA (γ-aminobutyric acid type A) in the amygdala, resulting in stronger negative feedback within fear circuitry and less anxious or fearful behaviour throughout adult life (Caldji, Diorio, & Meaney, 2003). Rat pups receiving high levels of maternal care show decreased DNA methylation in the promoter binding site for a transcription factor that accelerates the expression of Nr3c1, the gene that codes for the GR protein (see Textbox 3.3). The increased expression of GR in the hippocampal neurons of rat pups receiving abundant maternal care effectively reduces the production of CRF by the hypothalamus, resulting in diminished reactivity within the HPA axis. Variation in maternal care

experience also alters, probably through regulation of NMDA (N-methyl-D-aspartate) receptors, the production and plasticity of new inter-neuronal connections, which in turn are related to cognitive performance in hippocampal and prefrontal cortical areas (Meaney, Liu, Caldji, Sharma, & Plotsky, 2000).



(Hackman & Farah, 2009)

Textbox 3.3. Rat Model of epigenetics and the life course.

Epigenetic processes have been shown to account for the effects of maternal caregiving behaviour on the development and calibration of stress response systems in the newborn rat (Weaver et al., 2004). As shown in the figure above, pathways involving effects of the mother rat's licking and grooming of her pups are mediated by serotonin (5-HT) and a DNA transcription regulatory factor (nerve growth factor inducible A, NGFI-A), which guides the expression of the glucocorticoid receptor (GR) gene (Nr3c1) by binding to its promoter region.

In the pups of low licking and grooming mothers, the GR promoter is methylated, disallowing the activation of the gene by NGFI-A. This epigenetic regulatory process guides the responsivity or 'reactivity' of the hypothalamic-pituitary-adrenal endocrine axis and the production of glucocorticoids (principally cortisol in humans), one of the major stress response hormones.

It is important to recognize that, while these groundbreaking discoveries regarding the regulation of HPA reactivity focused principally on DNA methylation as the controlling epigenetic mark, a variety of other epigenetic mechanisms exist, including histone modification, nucleosome repositioning, and non-coding RNAs (Mehler, 2008). Nonetheless, the DNA methylation model of parental care epigenetically guiding the calibration of stress-responsive neural systems has offered a new level of biological plausibility to associations among early social environments, trajectories of normal and disordered development, and aspects of mental and physical health over the lifespan. Epigenetic processes appear to constitute one important class of mediators by which genes-environment interplay determines developmental and health outcomes (Champagne, 2010).

We have known for some time that our experience affects our development, learning and health and that this has consequences for society. Our genes do not determine our traits; rather there is a dynamic interplay between nature (genes) and nurture (environment). Recent advances in the areas of G x E interaction and epigenetics provide us with mechanisms that explain how this happens biologically. These mechanisms do not only explain how experience is embedded in our biology, but also how individual differences arise as a result of different experiences and/or different genetics. Previous research on single gene DNA polymorphisms has shown that depending on the form of the gene we inherit we will be more or less sensitive or resilient to early life adversities. But the developmental perspective is critical: how G x E interactions

change throughout development should be studied from a longitudinal perspective as discussed in the previous chapter. Genome-wide studies have the power to investigate how all the genes in our genome interact with early experience to shape our future development and health. Future research should investigate how gene polymorphisms interact with epigenetic mechanisms to further contribute to individual differences. Epigenetic regulation of the HPA axis provides a powerful model to investigate how gene expression in the stress axis changes as a result of early stress related to parenting. The epigenetic response to different extents of mother in rats can be viewed as an adaptive or a preparation for the future environments that the young pup will have to navigate in its life. Less licking by the mother upregulates the stress axis, making the pup more able to cope with unpredictable stressful environments, but incurring greater costs in terms of learning and health in later life. The next chapter focuses on the neurobiology of parenting.

6. Summary and conclusions

This chapter has explored and ordered recent literature linking frequent or severe exposures to early life adversities with the waning of health and failures of development, both in childhood and across the human lifespan. The following are its key take-home messages:

1. **Early adversity and later developmental health are linked through the structural and functional development of specific brain and peripheral nervous system circuits and pathways, most notably the stress response system, as well as through gene-regulating mechanisms.**

2. **There is converging evidence for the neurobiological plausibility of an early stress pathway to developmental health.** Brain circuits underlying the appraisal of threat, emotion regulation, self-control, and short-term memory, act in a coordinated way with the peripheral stress response systems to guide the overall stress response and maintain a dynamic balance in the organism. Under conditions of chronic stress, a persistent cost in stress regulation capacity is entailed with possible long-term repercussions for the general health status: i.e., impairments in immune function, increased rates of infectious and chronic diseases, higher blood pressure and risk of cardiovascular disease.

3. **There is substantial evidence that the stress-response system is plastic and extensively shaped by early experiences of stress and parental care.** Significant exposures to early adversity, especially those encountered in the context of family hardship and deprivation, may alter the structure and function of brain circuitry involved in the regulation of physiological stress.

4. **Health misfortune is non-randomly distributed within human populations**. Within every society on earth—small and large, primitive and advanced, simple and complex—subgroups of individuals sustain disproportionate shares of the population's overall burden of disease, injury and psychiatric morbidity. Differential exposures to early, socioeconomically partitioned stress and adversity account for a substantial portion of the unevenness in such distributions.

5. **Early exposures become 'biologically embedded' within a wide range of interconnected physiologic systems and at varying levels of scale and complexity, from the molecular to the systemic.** Further, evidence has rapidly accumulated linking experiences of childhood stress with the mental and physical disorders of adult life: a perspective that arguably renders all chronic morbidities to the category of 'developmental' disorders. Increasingly, we understand that what happens in childhood does not stay in childhood.

6. **Early adversity may impact developmental health in a variety of ways: through cumulative, progressive differential lifetime exposures, through some form of biological 'programming' whereby early insults become biologically embedded during sensitive periods in early development, and through developmental escalations in risk over time.** These models of early influence are not mutually exclusive, and each has empirical evidence pointing to its plausibility. The extent to which each of these models accounts for the association between early adversity and developmental health is still an object of debate.

7. **Our experience gets embedded in our biology through the mechanisms of G x E and epigenetics.** In G x E individuals with one form of a gene are less sensitive to early adversity than those with the other form of this gene. This leads to an individual's genotype (their DNA sequence) buffering the effect of early adversity. In epigenetics, the early adversity alters a gene's ability to make its mRNA and protein gene products. Epigenetics can be thought of as a dimmer switch that increases or decreases gene expression. **Future investigations should characterize the nature and timing of adversities that interact with the genome and the epigenome.** Genome wide analyses of G x E will further help identify which individuals are at risk and studies of differing epigenetic signatures among children from widely divergent early life circumstances will help better define which aspects of early nurturing environments have the capacity to biologically embed and influence developmental trajectories.

CHAPTER FOUR: PARENTING BEGETS PARENTING. A DEVELOPMENTAL PERSPECTIVE ON EARLY ADVERSITY AND THE TRANSMISSION OF PARENTING STYLES ACROSS GENERATIONS THROUGH NEUROPSYCHOLOGY, NEUROBIOLOGY, AND EPIGENETICS

The central question of this report is that of the putative role of ACE in the development of poor mental health and unhealthy behaviours. The previous chapters have addressed this question by examining longitudinal studies and by considering various development/biological processes that could account for the predictive associations between early ACE and negative developmental outcomes. Parenting is clearly part of this process; it is, after all, the main "proximal" environment for most children during their early development. The review of the evidence based on longitudinal studies strongly suggests that different forms of adverse parenting or, in some instances, the absence of a parent during early childhood, act as conditional determinants for a range of adjustment problems later in life. In this chapter we focus on parenting with special attention to how ACE and parenting may become associated over time and across generations, leading to negative developmental outcomes that can persist across multiple generations if intervening 'positive' influences do not redirect a child's developmental trajectory. Understanding how 'poor' parenting begets 'poor' parenting in the next generation is critical to the planning of timely interventions aimed at breaking up this intergenerational cycle of adversity. This chapter also points to features of positive parenting that create an environment in which healthy development can occur, but always with the view that both 'positive' and 'negative' parenting, as well as 'desirable' child outcomes cover a range of approaches, styles, and behaviours that vary across individuals, societies, and cultures (Hrdy et al., 2010; Keller, Borke, Yovsi, Lohaus, & Jensen, 2005; Keller et al., 2004).

Preliminary considerations

With a few possible and unfortunate exceptions, as in the studies associated with institutionalization (e.g., (Rutter et al., 2007)), the human literature relating early experiences and parenting is almost exclusively correlational. The behaviour of the caregiver or other forms of early adversity (ACE) experienced by the child are statistically correlated with measures taken on the child; early adversity is then said to be *associated with* aspects of child development. Strictly speaking in these instances, causality cannot be claimed. Therefore, when verbs like 'impact', 'contribute', 'affect' or 'influence' are used to describe the relation between experiences and outcomes, these should be understood to mean that there exists a correlation or an association, implying a statistical, not a mechanistic or causal, relation. This chapter also contains information derived from animal studies where early experiences and caregiving can be manipulated, allowing us to make stronger inferences of causality about the impact of early experiences on development of offspring. By exploring these animal studies as causal models and noting patterns in the effects of adversity that are comparable across species, by undertaking longitudinal studies with measures on parents, early environments, and child outcomes, and by exploiting the wealth of multilevel statistical approaches to the analysis of developmental data, we can begin to understand the causal relationships between early experiences and children's developmental trajectories.

The concept of normative-adaptive or species-typical parenting behaviour is implied throughout the chapter but we also acknowledge that among all species, especially humans, there are large individual and cultural differences in parenting behaviours and in feelings and attitudes towards infants, as well as in motivation to parent. In fact, individual differences are the hallmark of human behaviour within and across cultures, as well as over time, and it is the role of the scientist to study and disentangle the many factors, both environmental and genetic (and their interactions), which contribute to these individual differences.

Most of the research reviewed in this chapter focuses on factors that affect parenting by the mother, reflecting the state of the existing literature. Nevertheless, we recognize that fathers play a significant role in children's development. Specifically father's may influence cognitive (Sarkadi, Kristiansson, Oberklaid, & Bremberg, 2008; Tamis-LeMonda, Shannon, Cabrera, & Lamb, 2004) and social-emotional (Amato, 1994; Williams & Radin, 1999); (see also review by (Sarkadi et al., 2008)) development and father absence and/or harsh parenting is associated with the development of psychopathology, externalizing, and violent behaviours in boys (Chang, Schwartz, Dodge, & McBride-Chang, 2003; Côté et al., 2007). In addition, fathers and mothers exist within a family context, affect one another's parenting, and participate in a family dynamic that also contributes to children's development (Jenkins, Rasbash, Leckie, Gass, & Dunn, 2012; Meunier, Bisceglia, & Jenkins, 2012; Quinton & Rutter, 1984a, 1984b; Stover et al., 2012; Tamis-LeMonda et al., 2004). We reference these linkages between child outcomes and fathers' behaviour and family dynamics wherever possible.

In many homes and cultures, other relatives, friends, and professional caregivers also contribute to children's development (see (Hrdy et al., 2010)). Their caregiving is often associated with various and crucial aspects of development, as reflected in the growing literature on child-care relating to child development (NICHD Early Child Care Research Network, 2002; Peisner-Feinberg et al., 2001). In some circumstances, alloparents (i.e., non-biological caregivers) and child-care may buffer the negative outcomes associated with ACE and poor parenting (Côté et al., 2007; Geoffroy et al., 2010; Peisner-Feinberg et al., 2001). The NICHD Early Child Care Research Network has explored at some length the relative benefits for children of early child-care, remaining at home, and other caregiving arrangements (NICHD Early Child Care Research Network, 2005a, 2005b, 2005c, 2006). However, these forms of caregiving, while extremely important, are beyond the scope of the present report (Hrdy et al., 2010; Peisner-Feinberg et al., 2001).

Chapter plan

In most cases, a child's parents and immediate family provide the early and influential proximal environment through which a child's potential for "effective psychological function" begins to evolve and manifest (Bronfenbrenner & Ceci, 1994). It is those processes that occur in reciprocal interaction between a developing child and the "persons, objects, and symbols in its immediate environment" (Bronfenbrenner & Evans, 2000). Much of what has already been reviewed in previous chapters underscores the importance of children's early experiences in setting a child's developmental direction either as the first step in an interdependent chain of events on a life course or as events that embed themselves in the developing biology of the child to influence later life course outcomes (Hertzman & Boyce, 2010).

In this chapter we examine parenting, a parent's life history, particularly ACE, and the biology of parenting to understand how these influence the quality of parenting, a child's first proximal environment. In the first section (1) we review evidence for intergenerational repetition of parenting style. This is followed (2) by a description of the psychological mediators of parenting, including the role of mothers' perceptions, emotions, executive and cognitive function. Here, considerable attention is given to characterizing postpartum depression primarily in mothers, but also in fathers, and their effects on the offspring. The next section (3) focuses on what is known about the effects of different kinds of parenting and early adversity on infant development; we describe how positive warm attentive parenting, as well as early adversity in the form of neglect, abuse, and/or inconsistent care may predict developmental outcome in these same domains of emotion, perception, and executive function and their physiological underpinnings. This is followed by a review (4) of the physiological mediators associated with parenting including the role of hormones, key areas of the brain, and neurotransmitters. In the following section (5), we examine how early adversity influences these physiological mediators of parenting with particular attention to stress functions and development of the brain and neurochemistry. A final section (6) explores what is known about how specific genes and the early environment interact to predict parenting quality, and suggests the epigenetic mechanisms through which early experiences and adversity can affect the mechanisms of parenting. We close the chapter (7) with a brief summary of the material presented and some tentative conclusions aimed at informing targeted interventions to break intergenerational cycles of problematic parenting patterns.

1. Early experiences and intergenerational transfer of styles of mothering

There is a growing literature, both in animals and humans, showing that one of the most powerful predictors of the quality of mothering is how mothers were mothered themselves; that is, their own experiences growing up. In humans, important aspects of these early life experiences in the home are the warmth expressed by their mothers, whether the mother-infant interaction involved physical contact and play, visual mutuality, and/or vocal exchanges, and the extent to which mothers responded to their infant in a timely and appropriate way (that is, 'contingently') (Bornstein, Tamis-Lemonda, Hahn, & Haynes, 2008; Tamis-Lemonda & Bornstein, 1989; Tamis-Lemonda, Bornstein, & Baumwell, 2001). In non-human primates as well as in the rat, adequate maternal care has been shown to be necessary for the establishment of normal behavioural and physiological functioning in the offspring; variations in this care early in life—from complete maternal deprivation to identifying offspring exposed to a whole range of care conditions (e.g., in rat high vs. low licking/grooming reviewed in Chapter 3)—predict variations in a wide variety of developmental outcomes (Champagne, Francis, Mar, & Meaney, 2003; Champoux et al., 2002; Francis & Meaney, 1999; Maestripieri et al., 2006; Suomi, 1999). Among the most long-term of these outcomes, is the quality of maternal care offspring provide when adults.

a. Maternal history and parenting

Epidemiological studies demonstrate that children who are exposed to early adversity, including those associated with bonding and attachment, are at a higher risk for developing anxiety, depression, and other stress-related illnesses during adolescence (Martin, Bergen, Roeger, & Allison, 2004; McCauley et al., 1997; Rey, 1995) and adulthood (Enns, Cox, & Clara, 2002; Putnam, 2003). Spertus and colleagues (Spertus, Yehuda, Wong, Halligan, & Seremetis, 2003)

revealed that a woman's history of neglect and emotional abuse was related to increased depression, anxiety, posttraumatic stress and physical symptoms, and that some of these scars persisted over time, specifically, poorer physical and emotional functioning; factors that increased the risk for future difficulties in mothering. Moehler and colleagues (Moehler, Biringen, & Poustka, 2007) measured emotional availability during mother-infant interactions and found that mothers with a history of sexual or physical abuse were significantly more intrusive toward their children than were non-abused mothers. Roberts and colleagues (Roberts, O'Connor, Dunn, Golding, & ALSPAC Study Team, 2004) also report that mothers who had experienced sexual abuse in early life are less interested in becoming mothers themselves and when they do, exhibit impaired parenting skills, such as higher levels of child neglect, diminished confidence in their own parenting skills, more negative self-appraisal as a parent, greater use of physical punishment, and a lack of emotional control in parenting situations (Roberts et al., 2004). Knutson (Knutson, 1995) has reported that a substantial proportion of mothers who were abused during childhood go on to subsequently abuse their own children, when compared to mothers who did not report abuse.

Adjustment problems in offspring are often associated sequelae of cross-generational early abuse experiences. Using the Avon Longitudinal Study of Parents and Children, Collishaw et al (Collishaw, Dunn, O'Connor, & Golding, 2007) found that the more severely the mothers rated the impact of their own childhood maltreatment, the worse the adjustment of their offspring. Adjustment problems in offspring also were more chronic when mothers reported severe abuse than when they reported less severe adversity. Moreover, the effects were cumulative wherein problems in offspring were greater when maternal exposure was to several types of abuse as compared to only one type. Offspring of maltreated mothers also were at an increased risk of experiencing aversive events and physical assaults. Changes in the structure of their families, such as separations from caretakers and parents, and the acquisition of new parent figures, were more frequently reported. Finally, maltreated mothers' offspring also faced a wider range of stressful life events, such as moving into another neighbourhood, changing schools, and losing contact with friends.

Positive early experiences also predict later maternal behaviour (Belsky, Jaffee, Sligo, Woodward, & Silva, 2005; Chen & Kaplan, 2001b; Chen, Liu, & Kaplan, 2008). For instance, mothers who report positive childhood relationships with their parents are more responsive towards their children (Gara, Rosenberg, & Herzog, 1996). Furthermore, the experience of less authoritarian parents in early childhood, a more positive family 'climate' in middle childhood, and more positive attachment in adolescence, are all predictive of warm, sensitive, and stimulating maternal behaviour in adulthood (Belsky et al., 2005). In sum, early life experiences can be viewed as part of a spectrum from very negative to very positive, and both positive and negative parenting behaviours are transmitted inter-generationally (Bailey, Hill, Oesterle, & Hawkins, 2009; Belsky, Conger, & Capaldi, 2009; Conger, Belsky, & Capaldi, 2009; Neppl, Conger, Scaramella, & Ontai, 2009).

b. Intergenerational continuity of mothering

In rats and non-human primates, the early care infants receive from their mothers is a reliable predictor of the type of care they provide when they become mothers (Fleming et al., 2002;

Gonzalez, Lovic, Ward, Wainwright, & Fleming, 2001; Maestripieri, 2005; Maestripieri, Lindell, & Higley, 2007; Suomi, 1999). In human mothers, there is growing evidence as well for the intergenerational continuity of parenting style and quality (Bailey et al., 2009; Belsky et al., 2005; Chen & Kaplan, 2001a; Conger, Neppl, Kim, & Scaramella, 2003; Neppl et al., 2009; Scaramella, Neppl, Ontai, & Conger, 2008). The emphasis of this research has been both on the developmental sequelae of inadequate parenting and the outcomes associated with warm and supportive parenting. Initially relations were established by studies in which the early experiences were recalled retrospectively. Recently and more convincingly, studies have been prospective, in which families and children have been followed from childhood through adulthood (reviewed in (Belsky et al., 2009; Scaramella et al., 2008)). In many of these studies the quality of the mothering of the first generation (G1) and the second generation (G2) was observed directly.

Scaramella and colleagues (Scaramella et al., 2008) report a particularly informative prospective study of intergenerational parenting that eliminated bias associated with retrospective reports and had the advantage of a relatively large sample size (well over 100 subjects at each time point), direct behavioural observations and reliable coding, as well as independent characterizations of parents and adolescents allowing statistical separation of their individual contributions in parent-child interactions. Observations of parenting in the first and second generation showed a significant degree of continuity in both harsh and positive parenting among both males and females across the two generations. Harsh parenting in this context was defined as critical, aggressive, unkind, irritable, and 'pressureful' in a structured puzzle task. Positive parenting was defined as supportive, warm, helpful, and involved during the task. Harsh parenting was associated with 'externalizing' and disruptive behaviour in adolescents, whereas positive parenting was associated with competent behaviours in adolescents. The children displaying these behaviours as adolescents also tended to behave similarly as adults, which in turn may account for the differing parenting styles the adolescents exhibited as adults parenting their children (third generation). Because personality and behavioural characteristics of a child are also correlated with parenting, the study helps to disentangle the contributions of each factor of the parent-child interaction; for instance, the possibility that harsh parenting is associated with externalizing behaviours in a child, that then lead that child to become a harsh parent toward his/her own children. Hence, this study documents the important role of the child as a mediator in the apparent continuity of parenting.

These results are quite consistent with previous analyses and with other prospective studies of intergenerational transmission of parenting (Bailey et al., 2009; Belsky et al., 2009; Scaramella et al., 2008). It also implies that the problematic nature of some teenage mothering (de Paul & Domenech, 2000; Giardino, Gonzalez, Steiner, & Fleming, 2008; Rebollo & Montero, 2000) could be accounted for by an intergenerational process whereby teen mothers who raise poorly adjusted children then may in turn become poorly adjusted mothers (Furstenberg, Brooks-Gunn, & Morgan, 1987). The studies also point strongly to the critical nature of the parent-child interplay in long-term outcomes for offspring and to the bi-directional character of this developmental process. That is, parenting in early childhood may influence the child's developmental trajectory, but also, the child may influence the nature of parenting received through an interplay of social and/or genetic factors (see (Boivin et al., 2005)).

c. Buffers to the adverse effects of abuse

In spite of these apparent relations between early adversity, including physical abuse (and/or retrospective perception of that adversity), and later emotional and parental problems, it remains that a large proportion of mothers who were abused will NOT in turn abuse their own children. This suggests that a myriad of factors protect future mothers from the risks accrued through early experiences. Among these, social support to the mother or to the developing child (Jaffee, Caspi, Moffitt, Polo-Tomas, & Taylor, 2007; Kaufman et al., 2004; Wind & Silvern, 1994), as well as forming a relationship with a supportive partner in adulthood (Seeman, Singer, Ryff, Dienberg Love, & Levy-Storms, 2002), appear to play an important role. Supplying support to families at risk is indeed the basis for some effective preventive interventions reviewed in Chapter 5. Experiences during early developmental periods may well have greater impact than occurrences in later development periods (Heim & Nemeroff, 1999; McEwen, 2003), and form the stepping stones for the development of personal qualities underlying appropriate mothering, i.e., affect, attention, and learning. It also has been suggested that experiences acquired later in life can reverse previous effects, and/or result in development to follow a different path. McEwen (McEwen, 2003) in a review of the effects of early life adversity on brain development, concludes that problems brought about by unstable or abusive care-giving during childhood are not unavoidably irreversible, but may be ameliorated by a social support system or a caring and loving relationship with a partner.

2. Psychological mediators of mothering associated with early adversity

The underlying mechanisms linking early adversity and later mothering can be described at both the behavioural and physiological levels. For instance, in rats, mothers who received adequate parenting as neonates tend to show a balance in approach and avoidance behaviours in novel environments and with their pups; specifically, they show less fearfulness and enhanced attentiveness, and respond more positively to positive features of their young (summarized in Fleming & Li (Fleming & Li, 2002). These nurturing characteristics in the new mother are enhanced by the hormones associated with giving birth (progesterone, estrogen, prolactin, and oxytocin, see below); specifically hormones which enhance 'approach to pups' and reduce avoidance tendencies; as a result, these mothers are more able to interact effectively with their offspring (Fleming & Li, 2002; Numan, Fleming, & Levy, 2006). In contrast, early adversity and isolation rearing result in changes in the perceived value of environmental stimuli ('stimulus salience') (Lomanowska et al., 2011; Lomanowska, Rana, McCutcheon, Parker, & Wainwright, 2006), hyperactivity in activity tests (Gonzalez et al., 2001), increases in overall impulsivity (Lovic, Keen, Fletcher, & Fleming, 2011a; Lovic, Palombo, & Fleming, 2011b), reduced attention in an attention set-shifting task (Lovic & Fleming, 2004), as well as alterations in perceived reward value of pups (Afonso, King, Novakov, Burton, & Fleming, 2011; Afonso, King, Chatterjee, & Fleming, 2009). These psychological consequences of early adversity affect how the offspring will behave towards their own offspring when they grow up. Mothers showing reductions in levels of licking and crouching are more hyperactive, less attentive, more impulsive, and respond less positively to pups (summarized in (Barrett & Fleming, 2011)). In other words, early adversity can affect many aspects of behaviour. In turn, these psychological or behavioural effects can also affect how offspring interact with their own offspring in adulthood. A similar set of relations may apply to human mothers, as we describe below.

a. Reward processing, perception, and mothering

Infant-rewarding characteristics help sustain maternal responsiveness and motivation, and assure long-term maintenance of maternal interest in the baby. In animal models, attraction to infants is clearly facilitated by the hormones associated with parturition as well as by experience interacting with the young (Fleming & Li, 2002; Numan et al., 2006). However, soon after the very early postpartum period, the reward value of the young in sustaining subsequent behaviour is mediated by experience alone.

In humans, under optimal circumstances, the mother is attracted to her baby and with experience, reacts more positively towards infant cues and develops more nurturing attitudes (Fleming, Steiner, & Corter, 1997). For instance, in humans, even with little experience with their own in infants, new mothers find the infant body odor more pleasant than do non-mothers, and can recognize their own infants based on odor (summarized in (Barrett & Fleming, 2011; Corter & Fleming, 2002; Numan et al., 2006)). Visual cues also enhance mothering. When viewing silent videotapes of their infants, the sight of their own baby's smiling or crying causes heart-rate (HR) to decelerate, then accelerate (Wisenfeld, 1978) in parents, a pattern signaling their attentiveness to the infant cues. As well, in fMRI studies, pictures of one's own infant produces in mothers a pattern of brain activation in reward and emotion sites that is different from the pattern they show in response to the picture of an unfamiliar infant (Barrett & Fleming, 2011; Barrett et al., 2011). At the behavioural level, the infant's gaze evokes mother's gaze and leads to "en face" behaviour (where mother and baby look at one another, or at the least the mother looks into the baby's face), which Klaus, Trause, & Kennell (Klaus, Trause, & Kennell, 1975) described as species-typical maternal behaviour. Similarly, human mothers develop appropriate behavioural and physiological responses to infant cries, often experienced as aversive by non-parents. The cries of an infant signal need, and mothers often respond by approaching (Giardino et al., 2008; Stallings, Fleming, Corter, Worthman, & Steiner, 2001).

In short, mothering represents a motivated behaviour that interacts with mothers' own reward and affect systems, as well as with those of their children. There are large individual variations in the way in which very 'motivated' mothers respond to their infants and, in turn, in the ways infants themselves respond. Appropriate responsiveness requires that mothers be affectively prepared to interact with their new infants, which, unfortunately, is not always the case. The next section describes how the psychological state-of-mind, in particular, depressed mood, or disphoria may impact parenting during the early postpartum period.

b. Depressed mood and mothering

For many women the first week postpartum is a positive and exciting experience, that maps on to countless changes in the mothers' awareness of her new role and the subsequent experience of 'falling-in-love' with her baby, along with all the anxiety and happiness that are normally involved. Fleming and colleagues have illustrated the development of these robust positive feelings of nurturance—and associated anxiety—as they take place across pregnancy and throughout the first year postpartum (Corter & Fleming, 2002).

In contrast to these positive feelings, a substantial number of women experience negative feelings during the first few postpartum months (Friedman & Resnick, 2008; Gale & Harlow, 2003; Marcus, 2009). Up to 20% of women exhibit symptoms of depression in the first weeks following delivery (Gavin et al., 2005; Marcus, 2009). The incidence rises within 30 days post-partum and, in most cases, these depressive episodes resolve spontaneously within six months to a year. However, in a few cases, they may persist for two years (Cooper & Murray, 1995; Cox, Murray, & Chapman, 1993). The profile of symptoms of postpartum depression includes sad mood, impaired concentration, and restlessness/agitation, resembling that of a major depressive episode experienced at other times in life. However, its timing is distinctive in that it typically affects the mother-baby relationship and, in many cases, the entire family unit. Interestingly, evidence suggests greater psychomotor disturbance (as shown, for example, by a reduced capacity to drive a car safely) further distinguishing postpartum depression from other forms of depression (Bernstein et al., 2008).

Many factors have been associated with both mothers' and fathers' susceptibility in developing depression in the postpartum period (see (Goodman, 2004; Kentner, Abizaid, & Bielajew, 2010)) including the life-time history of depression, type of delivery, infant colic, seasonal factors, maternal sleep, lack of social support, SES, recent stressful life events, marital conflict, and the development of a parent's 'stress' system, to name a few (Boyce & Todd, 1992; Goyal, Gay, & Lee, 2009; Koo, Lynch, & Cooper, 2003; Panthangi, West, Savoy-Moore, Geeta, & Reickert, 2009; Vik et al., 2009; Xie, He, Koszycki, Walker, & Wen, 2009). Postpartum depression is thus a complex phenomenon related to many interdependent factors. Not surprisingly, one of the chief risk factors for the development of depression in adulthood, outside of the postpartum period, is a history of childhood adversity (with the caveat that it is often assessed through recall), including parenting factors such as insecure attachment, abuse, lack of warmth, and parental rejection ((Heim, Plotsky, & Nemeroff, 2004; Karevold et al., 2009); reviewed in (Penza, Heim, & Nemeroff, 2003)).

As with other forms of depression, postpartum depression is often co-morbid with other psychiatric disorders, such as generalized anxiety disorder, obsessive-compulsive disorder, social phobia and agoraphobia (fear of wide open spaces, crowds, or uncontrolled social conditions) (Figueira, Fernandes Malloy-Diniz, Aurélio Romano-Silva, Silva Neves, & Corrêa, 2009). In some rare and extreme instances, postpartum depression has been associated with suicidality and the murdering of offspring (Kauppi, Kumpulainen, Vanamo, Merikanto, & Karkola, 2008; Paris, Bolton, & Weinberg, 2009).

As many as half of postpartum depression cases are undiagnosed, partly due to a lack of attention given to the mental health of the mother by health care providers, as well as mothers' under-reporting of symptoms (Chaudron et al., 2005; Murray, Wooglar, Murray, & Cooper, 2003). This chilling statistic is a source of concern for the health of the mother and the child as depressed mothers also tend to be less attentive mothers, as reviewed in the following section.

c. Maternal depressed mood and mother-infant relationship

Mothers with postpartum depression are more likely to be more irritated and intrusive, and respond with less contingency and sensitivity to their newborns. Compared to mothers without postpartum depression, they also are likely to respond more negatively to their infant and demonstrate disrupted patterns of communication (Beebe et al., 2008; Chung, McCollum, Elo, Lee, & Culhane, 2004; Feldman & Eidelman, 2007; Herrera, Reissland, & Shepherd, 2004; Milgrom & Westley, 2004; Paris et al., 2009; Righetti-Veltema, Conne-Perréard, Bousquet, & Manzano, 2002); for a review see (Field, Diego, & Hernandez-Reif, 2009). Depressed dyads (i.e., mother-baby pairs) exhibit a reduced mutual attentiveness, touching and interactions or smiling, vocal and visual communications, compared to postpartum non-depression dyads (Field, 1990; Fleming, Ruble, Flett, & Shaul, 1988; Righetti-Veltema et al., 2002) later in the postpartum period. For example, in a recent study, Field and colleagues (Field et al., 2007) found that, compared to non-depressed mothers, mothers with postpartum depression were less interactive with their four-month-old infants at baseline before adopting a "still face" in an experimental procedure (i.e., mother is instructed to maintain a neutral expression while looking at the baby for a 2-minute period, regardless of what the infant does, before returning to a normal interaction), as well as during the reunion period after the still face episode. The latter finding is especially telling as the key feature of the period of reunion in the still-face paradigm is to try to reinstate a more positive interaction and regulate the emotion of the infant. More practically, maternal activities such as bedtime routines, breastfeeding, and medical care also seem affected by depression (Field et al., 2009).

d. Early adversity, parents' depression, and emotional development

Not surprisingly, postpartum depression in mothers and fathers also has implications for the infant (Goodman & Gotlib, 2002; Kane & Garber, 2004; Tronick & Reck, 2009). Infants of depressed mothers are less interactive (Field et al., 2007), socially engaged (Feldman, Granat, Pariente, & Kanety, 2009) and show more negative emotionality (Feldman et al., 2009). In addition, there is some evidence for an association between maternal depression and infant cognitive and motor development (Tronick & Reck, 2009). Field and colleagues (reviewed in (Field et al., 2009)) have shown that in the early postpartum period, infants of depressed mothers are less responsive to, and show less interest in faces and voices. These findings could reflect higher arousal levels, less attentiveness, and perhaps altered sociability and empathy in the child. Infants of depressed mothers exhibit a distinct physiological profile, one that also is associated with heightened stress (Diego et al., 2004; Diego, Field, Jones, & Hernadez-Reif, 2006; Diego, Jones, & Field, 2010; Field & Goodman, 2002). Maternal depression (even after it is in remission) has also been associated with physiological, cognitive, behavioural and emotional functioning across the lifespan of children, including an increased risk of developing psychopathology in adolescence or young adulthood (Brand & Brennan, 2009; Cicchetti et al., 1998; Gump et al., 2009; Halligan, Murray, Martins, & Cooper, 2007).

Associations of fathers' mood with child outcomes also appear in studies of fathering. Although not frequently studied, there is growing evidence that 5 to 10% of new fathers (as opposed to 15-20% of new mothers) become depressed during the first postnatal year and this depression is associated with paternal behaviour. In one small study, father depression was related to more

spanking of the child, as well as less often reading or engaging positively with the child (Davis, Davis, Freed, & Clark, 2011). In a large community sample, paternal depression later in a child's life also has been associated with greater paternal hostility towards the adolescent. Among girls, this paternal depression was associated with greater perceived father hostility, and greater adolescent psychopathology, a relationship that held once demographic factors and mothers' depressive symptoms were taken into account. Finally, Flouri and colleagues (McEwen & Flouri, 2009; Walton & Flouri, 2010) found that the behaviour of fathers and mothers was associated with different aspects of adolescent emotion regulation, with maternal warmth being positively related to good regulation and psychological control being negatively related. Other results (Ramchandani, Stein, Evans, & O'Connor, 2005; Ramchandani, Stein, Hotopf, & Wiles, 2006), also suggest that father's depression or antisocial behaviour is strongly predictive of child internalizing and externalizing disorders; after controlling for maternal depression and anxiety, paternal depression during the perinatal period or anxiety through the first postnatal year were associated with a higher risk of conduct problems in boys (Ramchandani et al., 2005), and with later childhood recurring abdominal pain, respectively (Ramchandani et al., 2006). Whereas children's internalizing behaviour is more closely associated with maternal depression and psychopathology, children's externalizing behaviour is related to psychopathology in both parents (Connell & Goodman, 2002). Based on these studies it is clear that both maternal and paternal affective disorders may impact the child. Not surprisingly then, when they co-occur, they seem to combine to adversely influence adolescent emotional development (Reeb, Conger, & Wu, 2010), often making significant and independent contributions (Marmorstein, Malone, & Iacono, 2004).

Early adversity also plays a significant role in the development of depression. Specifically, early adversity has been related to earlier onset of depression, a greater number of depressive episodes, a more chronic course of the illness and a greater likelihood of suicide (Bernet & Stein, 1999; Bifulco, Moran, Baines, Bunn, & Stanford, 2002; Brown & Moran, 1994; Brown, Cohen, Johnson, & Smailes, 1999; Harkness & Monroe, 2002; Lizardi et al., 1995; McCauley et al., 1997; Moskvina et al., 2007). The timing of early adversity (earlier in childhood is considered a more vulnerable period), gender (men are less vulnerable), stressful life experiences and HPA axis functioning throughout life, as well as genetic characteristics (Heim & Nemeroff, 1999; Heim et al., 2004) are all factors that moderate and/or mediate the relationship between early adversity and depression.

Taken together, these studies indicate that depression in the parents is associated with a variety of problematic child outcomes and this relation holds for depression in both mothers and fathers. As described above, studies relating mothers' depression and difficult parenting to child outcomes indicate the importance of these environmentally mediated influences, over and above a genetic liability for poor outcomes shared by parents and children. This parent-child association is robust in that it has been documented across a number of different types of study designs (prospective longitudinal, retrospective, high-risk, and the 'new generation studies') and populations (e.g., high risk, court involved, etc.). Hence, in terms of understanding where to look for effective interventions in parenting, it is clear that both mothers and fathers' mood states and emotion regulation need to be considered.

e. Cognition, attention, and mothering

In addition to being emotionally prepared, mothers must also be able to attend to their infants; they must be able to inhibit inappropriate responses and to organize themselves around the many needs of the child. Planning, organization, flexibility, attention are all aspects of cognitive function or *executive function*, that mothers depend on to be appropriately responsive to babies and children. These cognitive characteristics are regulated in large part by the frontal cortex and are subsumed under the label of prefrontal function. Prefrontal cortex is a brain region in the front of the cerebral cortex that receives projections from many areas of the brain, but especially from the reward system, emotion systems, and systems that regulate cognitive function. This is true in animals where there exists a strong positive relation between rat mothers' licking behaviour and her ability to shift attention (Lovic & Fleming, 2004), to inhibit responses to irrelevant aspects of the environment (Lovic & Fleming, 2004), and to reduce motor impulsivity (Lovic et al., 2011b). In a recent study of human mothers, Gonzalez and colleagues (Gonzalez, Jenkins, Steiner, & Fleming, 2012) found that mothers who showed good working memory and attention responded more 'contingently' and sensitively to their infants. They also showed reduced chronic levels of cortisol, which were also related to the quality of mothering (Gonzalez et al., 2012). Interestingly a similar relation may also hold for fathers for whom there is evidence that high levels of impulsivity and inattention predicts "lax parenting, over-activity and argumentativeness when interacting with their child" (Harvey, Danforth, McKee, Ulaszek, & Friedman, 2003).

In light of these findings on adult mothers and fathers, it is not surprising that teenage mothers, who tend to have reduced executive function abilities, poorer attention and lower impulse control and flexibility (Chico, Gonzalez, Wonch, & Fleming, 2010), (Klaus et al., 1975), also tend to be less sensitive when interacting with their six-month-old babies. In addition to healthy executive function and a balanced emotional state, parents also must develop a good sense of their infants' needs and desires and show empathy and an appreciation for the baby as having an independent mind. These are qualities that have been associated with early childhood experiences as we now discuss.

3. Effects of early adversity and parenting on infant development in perceptual, affective, and cognitive domains

a. Early adversity and perceptual responsiveness

Early adversity has been associated with heightened responsiveness to all stimuli, but also with a bias towards stimuli with negative valence. Children who were abused and/or neglected show a negative bias, and are more attentive to negative pictures than to positive pictures. Measuring brain electrical responses through event response potentials (ERP), a measure of neural activity, Pollak and his colleagues (Pollak, Cicchetti, Klorman, & Brumaghim, 1997; Pollak, Klorman, Thatcher, & Cicchetti, 2001) have shown that one of the wave forms of the ERP, the P3b component, which reflects attention and interest, has a greater amplitude in abused, as opposed to non-abused, children when they are presented with an angry face or vocal expressions of anger, and especially faces of their own mothers. The amplitude of P3b also has been associated with the severity of physical maltreatment

(Pollak et al., 1997; Pollak et al., 2001; Shackman, Shackman, & Pollak, 2007). Such a pattern of association was not shown when happy faces were shown. Moreover, abused children had more difficulties disengaging from attending to angry faces even when they were instructed to avoid them. As a result, they do worse on neutral goal-directed tasks in the presence of an angry face (Shackman et al., 2007).

These difficulties in emotion and social regulation associated with early adversity suggest that some children develop an emotional style that predisposes them to be emotionally reactive to the environment and to adopt a more negative world view later in life. However, it is not clear whether this emotional style relates to their future parental sensitivity. Other psychological features linked to emotion, cognition and attention, could also be involved in the developmental cycle linking experiences of early adversity and quality of later mothering. These are important to consider because animal models (i.e., rats) have shown that early adversity puts mothers at greater risk for problems with impulse control, attention, and cognitive function. As reviewed above, in both rats and humans, impulsive and inattentive mothers have greater difficulty interacting contingently and sensitively with their infants.

We now turn to the emotional reactions of children as they relate to their own earlier experiences, with a view to illustrating how early experiences may relate to the development of the emotion regulation system in children. These, in turn, are likely the precursors to later emotion regulation in adulthood and affecting maternal sensitivity.

b. Early adversity and executive function

In both the animal and human literature there is strong evidence showing that maternal deprivation during an offspring's early years results in poor development of many of the executive functions that are necessary for well-regulated mothering. In rats, for instance, being reared without the mother results in offspring that show deficits in executive function-processes associated with attention and ability to shift attention when needed (Burton, Lovic, & Fleming, 2006; Garner, Wood, Pantelis, & van den Buuse, 2007; Lovic & Fleming, 2004). Early adversity studies in children have found a stable relationship between abuse or neglect and executive function (Bos, Fox, Zeanah, & Nelson, 2009; De Bellis, 2005; Kreppner, O'Connor, & Rutter, 2001; Pears & Fisher, 2005). Bos and colleagues (Bos et al., 2009) investigated executive function in children that had a history of early deprivation due to institutionalization and reported that early adversity is associated with deficits in performance on tasks that involve planning and working memory. Early adversity resulting from familial violence has also been associated with deficits in a wide range of executive functions, including working memory, problem solving, inhibition and attentional control (Fishbein et al., 2009; Nolin & Ethier, 2007; Pears, Kim, & Fisher, 2008). While we expect that these deficits continue into adulthood, less is known about the predictive relationship between early adversity and executive function in adulthood. Although results have been mixed (see (Rogers et al., 2004)), deficits in executive function such as working memory and set-shifting have been linked to major depression and other affective disorders in adults (Fossati, Ergis, & Allilaire, 2001). These functions, as we have seen, are closely related to appropriate mothering.

Thus for both perceptual responsiveness and executive functions, there is evidence of a link between early adversity, defined as inappropriate or abusive parenting, and deficits in these cognitive functions. These cognitive functions are obviously relevant for parenting, but factual data linking early adversity (i.e., parenting), these cognitive functions, and later parenting is lacking at this point.

Another possible set of mediators linking early adversity and later mothering are found in the stress response physiological pathways. It is to these processes that we now turn

4. Physiological mediators of mothering and their association with early adversity

a. Hormones and mothering (and fathering)

As alluded to previously, in most mammalian species that have been studied, the hormones associated with late pregnancy and childbirth enhance the likelihood that the new mother will respond appropriately to her newborn offspring. Mothers undergo a shift from being non-responsive to acting responsively over the course of a short period before, during and after birth (Numan et al., 2006). The hormones that are implicated in this process vary across species, but most involve a configuration of hormones, including elevations in estrogen, and then prolactin and oxytocin, against a background of declining gestational progesterone (Numan et al., 2006). The well-known peptide oxytocin (primed by estrogens and affected by the glucocorticoids) has also been strongly implicated in the activation of nurturance in many species, including humans (Bardi, Shimizu, Barrett, Borgognini-Tarli, & Huffman, 2003; Feldman, Gordon, Schneiderman, Weisman, & Zagoory-Sharon, 2010; Feldman, Gordon, & Zagoory-Sharon, 2010; Gordon, Zagoory-Sharon, Leckman, & Feldman, 2010a, 2010b; Numan et al., 2006).

Although most mammalian species are not bi-parental, as fathers do not engage in paternal behaviour, some are and pair-bond during the period of dual parenting. In these cases, there is evidence that the hormones prolactin, oxytocin, and testosterone are implicated in responsiveness to young, oxytocin and prolactin by enhancing behaviour and testosterone, by having an inhibitory effect (Kentner et al., 2010). In humans as well, there is evidence of an inverse relationship between the paternal state when interacting with their young and, also with increasing testosterone. For mothers, there is a positive relation between measures of paternal responsiveness and both prolactin and oxytocin (Berg & Wynne-Edwards, 2001; Delahunty, McKay, Noseworthy, & Storey, 2007; Fleming, 2002; Kentner et al., 2010; Storey, Noseworthy, Delahunty, Halfyard, & McKay, 2011; Storey, Walsh, Quinton, & Wynne-Edwards, 2000).

Once animals become 'biologically motivated' to respond maternally to their young, the quality of the behaviour they exhibit is not strongly affected by hormones, but is primarily experience based. Hormones, however, especially those of the HPA can affect the intensity of maternal behaviour: corticosterone in rats and cortisol in humans. This system is important both in normal functioning and dysregulation of behaviour. Below we discuss the role of this system in mothering.

b. Stress hormones and mothering

The hypothalamic-pituitary-adrenal (HPA) axis or 'stress' system is a hormonal system critical for physiological adjustments to environmental challenges and 'stresses'. The HPA axis is key in regulating metabolism to insure energy availability for action and proper immune function, as well as having mobilizing effects to enhance attention and memory. It is also a system that has adverse effects on the brain and body when activated without relief over long periods of time. Chronic stress can cause a complete shutdown of the HPA system, producing changes in metabolism, disease susceptibility, in other aspects of physiology and in normal behaviour.

There is substantial evidence that the HPA axis has both an activating and inhibitory effect on the maternal system, depending on the stage of postpartum, the parity and endocrine condition of the female, and an animal's earlier experiences (see (Brummelte & Galea, 2010; Numan et al., 2006; Rees, Panesar, Steiner, & Fleming, 2006)). In human mothers, postpartum cortisol concentrations soon after birth—which are extraordinarily high—are positively associated with many nurturing features of mothering. Women experiencing higher levels of corticosterone engage in more contact with their babies, find baby odors to be more attractive, are better able to recognize their babies based on their odors, are more sympathetic when exposed to infant cries, and show altogether heightened feelings of wellbeing (Fleming et al., 1997; Giardino et al., 2008; Krpan, Coombs, Zinga, Steiner, & Fleming, 2005; Stallings et al., 2001), (summarized in (Corter & Fleming, 2002; Numan et al., 2006)). Later in the postpartum period, when the priming effects of the childbirth hormones are no longer present, high cortisol does not appear to directly impact maternal behaviour itself in humans. Research in monkeys suggest that high cortisol at this time is quite deleterious to appropriate mothering, especially in the context of the childbirth hormones (Bardi, Bode, Ramirez, & Brent, 2005). This bimodal effect of cortisol has been demonstrated in a variety of contexts and suggests that a certain level may be necessary for alertness and adequate attention to young, especially if acting within the context of hormonal priming by progesterone and estrogen. However, if the levels are too high and hormonal priming is no longer present, maternal behaviour can be disrupted (see (Brummelte & Galea, 2010; Rees et al., 2006)). As discussed previously, regulation of the HPA system is clearly affected by ACE, and the resulting dysregulation in the mother could impact her mood, attention, and the intensity or quality of mothering she exhibits.

c. Stress hormones and postpartum depression

Although there is strong evidence of a relationship between depression and cortisol outside of the postpartum period (Gunnar & Fisher, 2006; Heim et al., 2004; Neigh, Gillespie, & Nemeroff, 2009), the evidence is mixed regarding the role of the HPA stress system in the regulation of postpartum depression. Increased plasma cortisol levels have been associated with partum depression in some studies, but not in others (Groer & Moran, 2007; Jolley, Elmore, Barnard, & Carr, 2007; Kammerer, Taylor, & Glover, 2006; Nierop, Bratsikas, Zimmermann, & Ehlert, 2006). In some studies, it also has been associated with positive affect (Groer, 2005). As with mothering per se, whether the relation between affect and cortisol levels is positive or negative depends on a variety of factors (Corter & Fleming, 2002; Numan et al., 2006): (a) the mothers' age; in teen mothers high levels of cortisol are associated with more energy and greater feelings of wellbeing, whereas in older mothers high cortisol is associated with fatigue and negative

affect; (b) the postpartum period; in older mothers, cortisol levels have a positive relation with maternal mood on postpartum days two to four, but a negative relation at three to four months postpartum; (c) the context for cortisol elevation; in the absence of stressors the relation may be positive, but if associated with prior stressors, cortisol is related to negative mood; and (d) whether cortisol is measured in the morning, evening, or throughout the day and whether the levels reflect a clear stress response. These different sets of correlations demonstrate that in different contexts, ages, and possibly according to variations in other "stress" hormones released along with cortisol (parasympathetic and sympathetic hormones and/or neurochemicals), the relations with mood state will differ. Since one of the primary predictors of postpartum depression is depression earlier in life, the manner in which the HPA axis is regulated likely sets the stage for emotion regulation postpartum.

Hormonal effects on mothering occur through their actions on neurotransmitters and brain systems that affect mothering. The role of the neurotransmitters in mothering has been demonstrated predominantly in animal models. The neural circuitry on which these transmitters act has been explored both in animals and in humans. Some of these studies are described in the following section.

d. The brain, neurotransmitters and mothering

What we know about the maternal brain and its neural circuitry is derived almost exclusively from experimental research based on lesion, stimulation, and pharmacologic studies with rat and monkey (Barrett & Fleming, 2011; Fleming & Li, 2002; Numan et al., 2006). Broadly speaking, this body of work shows that the circuitry involves lower-level systems in the hypothalamus and midbrain that can be thought of as the 'final common path' for the expression of maternal behaviours. Interconnecting this system are projections from limbic structures, including the olfactory system, the amygdala, and the nucleus accumbens that mediate the expression of olfactory-based hedonics, affect, and reward processing, respectively. Intersecting with both the hypothalamic and the limbic systems are cortical systems, including the prefrontal, orbitofrontal, and cingulate systems that regulate planning, attention, working memory and social-emotional expression. See Figure 4.1 for a schematic of this maternal circuitry in the rat.

Within the past five years there have been a plethora of human fMRI studies focusing on the brain activation patterns of mothers and others to infant related stimuli presented while a person is in the fMRI machine. These studies show a pattern of activation in humans that matches quite well the pattern derived from animal experimental studies, with activation in limbic structures, but especially in cortical structures (Bartels & Zeki, 2004; Leibenluft, Gobbini, Harrison, & Haxby, 2004; Seifritz et al., 2003; Swain, 2008; Swain & Hoa, 2010). For example, focusing quite directly on sites within the brain known to be important among other mammals, Barrett and colleagues (see (Barrett & Fleming, 2011; Barrett et al., 2011)) presented pictures of their own infants and other infants to new mothers. They found that mothers responded most positively to faces of their own infants smiling (as opposed to crying) and that the brain areas that became activated to the familiarity dimension and affect dimensions of their own infant faces compared to the control condition included many of the same sites described in the animal models, including the nucleus accumbens, the amygdala, and the cingulated cortex. See Figure 4.2 for a schematic of the proposed maternal circuitry in humans.

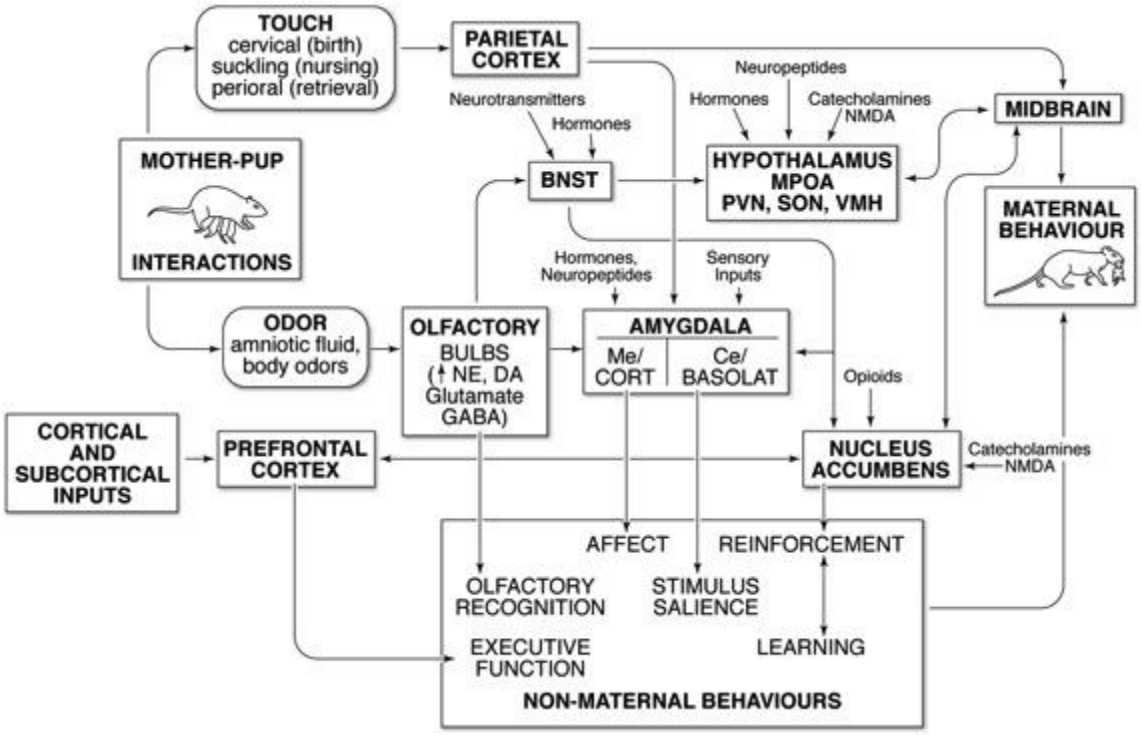


Figure 4.1. Functional neuroanatomy mediating maternal and related behaviours in mammals. *Neuroanatomical structures include olfactory bulbs, amygdala, nucleus accumbens, bed nucleus of the stria terminalis (BNST), medial preoptic area (MPOA), ventromedial hypothalamus (VMH), periventricular nucleus (PVN), supraoptic nucleus (SON), midbrain, and parietal cortex. Relevant neurochemistry includes the catecholamines, NE, and dopamine (DA), the neuropeptides, and the opioids (Barrett & Fleming, 2011).*

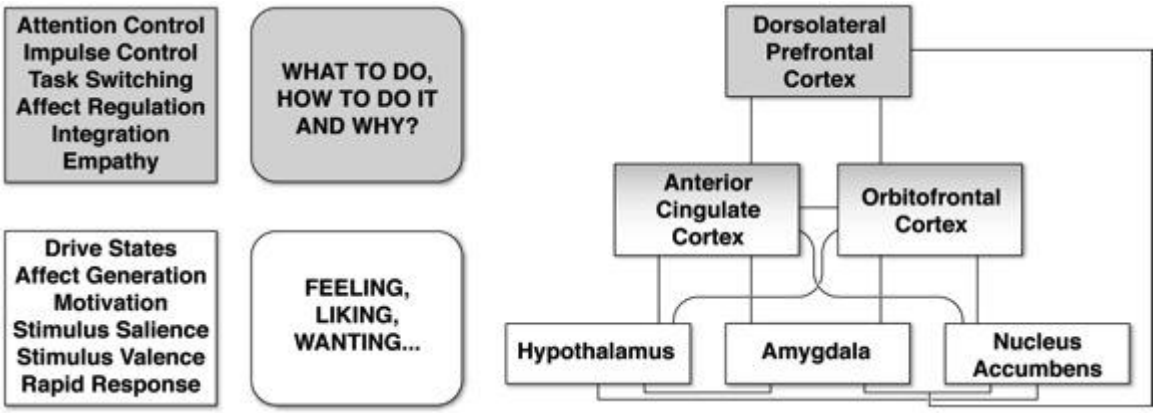


Figure 4.2. Schematic of a putative human maternal circuit. *Brain regions known or believed to be important in human maternal behaviour serve a number of important functions. There are (relatively) gross subcortical functions related to reward, affect, and motivation that serve to ensure that the baby is a strongly positively reinforcing stimulus that the mother is driven to care for, be responsive to, and show affection to. There are also higher-order cortical functions that regulate maternal behaviour in the context of the (internal and external) environment and in light of overarching goals, standards, mores, and intentions. Some regions, namely the anterior cingulate cortex and orbitofrontal cortex, operate at the interface of the two systems (Barrett & Fleming, 2011).*

It is important to remember that the brain and neurotransmitter systems that become activated by infant stimulation in new mothers are **not** specific to mothering or to infants; instead they reflect

activation of general processes that are recruited, utilized, or activated by different stimuli at different life stages and under different endocrine, experiential, and motivational conditions. Below we discuss two brain systems that are heavily implicated in mothers' responses to their offspring and are also affected by early experiences.

e. Brain, reward and dopamine

While many neurotransmitters play a role in the onset of mothering, dopamine, a major catecholaminergic neurotransmitter in the brain and perhaps the most studied of the neurotransmitters, has been clearly implicated in reward, mood, attention, and mothering at least in non-humans. The general function of dopamine is to reflect and enhance the rewarding properties or salience of stimuli for an animal. Depending on an animal's 'motivational' state, relevant stimuli are food to the hungry animal, a sexually experienced male for an estrous females, or pups for a new mother (Afonso et al., 2011; Afonso, Grella, Chatterjee, & Fleming, 2008; Afonso et al., 2009; Berridge & Robinson, 1998). In the new mother rat, hormones progesterone and estrogen suppress baseline activity of the dopamine system in the nucleus accumbens. In hormonally primed new mother rats subsequent pup stimulation produces an increase in dopamine over baseline which is proportionally greater than it would be if the baseline were high. Therefore, this hormonal effect acts to tune the dopamine system by enhancing the ratio of dopamine signal to baseline noise when pups are presented (Afonso et al., 2011).

f. Brain and affect, stimulus salience and attention

Another system that has been studied heavily is the limbic-amygdala system, known for its involvement in emotion regulation, fear expression, fear conditioning, and affect in general (Hartley, Fischl, & Phelps, 2011; Mitra & Sapolsky, 2010a, 2010b). It is also implicated in the change the new mother rat undergoes during parturition when she transforms herself from an animal that is fearful and withdraws from young into one that approaches and engages with the young (see (Fleming & Li, 2002; Numan et al., 2006)). As indicated above, in humans, functional magnetic resonance imaging (fMRI) studies of emotion similarly focus attention on the amygdala, as well as the cingulate cortex (Barrett & Fleming, 2011). Mothers show a greater response (functional BOLD imaging) to happy over unhappy faces of their own infants in the amygdala and show a response pattern that relates quite clearly to their levels of anxiety and depression (Barrett et al., 2011). In rat, reducing fear and withdrawal is normally accomplished at the time of parturition by hormones, likely acting at the level of the amygdala.

Now that we have reviewed the role of hormones, the brain, and the neurotransmitter systems necessary for mothering behaviour, the next question and essential to the purposes of this report is: to what extent and how do early experiences impact these systems to disrupt later mothering?

5. Early adversity and effects on physiological mediators of mothering

a. Early adversity and development of stress function

There is little doubt that early adversity and pre- and postnatal experiences or ACE can result in a heightened stress reactivity in the offspring that in many cases can persist into adulthood.

b. Prenatal adversity

Numerous studies in animals have described the effects of manipulating the maternal/fetal environment on stress responsiveness, (acting through the HPA axis and sympathetic nervous system) and behaviours (e.g. locomotor activity, learning & memory) in later life. These studies have been comprehensively reviewed with the general consensus that stress applied experimentally (restraint stress as one example) during pregnancy leads to increased HPA activity in guinea pig, rat, and primate offspring (Bergman, Sarkar, Glover, & O'Connor, 2010; Cottrell & Seckl, 2009; Kapoor, Dunn, Kostaki, Andrews, & Matthews, 2006; Kapoor & Matthews, 2008; Weinstock, 2008). These studies have also demonstrated that the timing in gestation when maternal adversity occurs has a major impact on the offspring HPA system functioning later in life (Kapoor & Matthews, 2005). The outcomes also seem to be greatly dependent on the age of outcome assessment, offspring sex and, in females, the phase of the menstrual cycle at which a given outcome is measured (Kapoor & Matthews, 2008).

Several studies have now assessed the association between stressful experiences during pregnancy and HPA function in children (Glover, O'Connor, & O'Donnell, 2010; Tollenaar, Beijers, Jansen, Riksen-Walraven, & de Weerth, 2011). The adverse maternal experiences that have been summarized in these studies are comprised of measures of 'daily hassles', life events (moving to a new house, death of a family member and so on) or domestic violence. An emerging consensus is that maternal stress is associated with a wide range of neuroendocrine disturbances in the offspring and related adverse developmental outcomes that include altered behaviour (Weinstock, 2008). A longitudinal study of mothers and their children suggested that maternal anxiety (self-reports) during late pregnancy predicted a higher awakening salivary cortisol secretion in the offspring at ten years of age (O'Connor et al., 2005). The prediction persisted after accounting for socio-demographic and obstetric factors, that included several postnatal assessments of maternal depression and anxiety. Another study from the Netherlands demonstrated that prenatal anxiety (as indicated by fear about pregnancy outcome or giving birth and daily hassles,) at gestation week 16 was related to higher cortisol responses to vaccination in five year old offspring (Gutteling, de Weerth, & Buitelaar, 2005). High prenatal maternal cortisol levels were also associated with cortisol responses in the offspring. Further evidence also comes from a retrospective study of healthy young adults whose mothers reported different stressors such as death of, or severe illness of, a close relative during their pregnancy (Entringer et al., 2009). However, given that these cortisol responses were related to naturally occurring stress or to the perception of stress, and as in some studies stress in mothers is associated with stress in children, it is not possible to dissociate the direction of causality if such exists or the role of shared genetic effects.

c. Postnatal adversity

Evidence from animal studies suggests that maternal separation and the quality of maternal care alters the development of several endocrine systems, including the HPA axis (Champagne & Meaney, 2001). Rat mothers that were raised without their mothers or raised by mothers that showed low levels of maternal licking demonstrated elevated stress activated HPA function (Belay et al., 2011; Burton et al., 2007; Francis, Diorio, Liu, & Meaney, 1999). Studies of early adversity in primates, where maternal separation or stress paradigms that more closely resemble that of human mothers and infants, have led to more varied results; some studies demonstrating HPA-axis hypoactivity (Coplan et al., 1995; Rosenblum et al., 1994; Rosenblum et al., 2002) and others HPA hyperactivity (Fahlke et al., 2000; Higley et al., 1992; Higley, Suomi, & Linnoila, 1991).

Some humans experience early adversity in the family of origin, as well as persistent and systemic adversity associated with chronic family dysfunction, low SES, and/or with inadequate social support. Hertzman & Boyce (Hertzman & Boyce, 2010) have summarized results showing that a low socioeconomic position over a lifetime is associated with a substantial increase in the awakening cortisol levels, an 8%-10% increase in cumulative cortisol secretion during the early day hour, and an increased risk by 60%-91% of having an abnormal cortisol secretion pattern. Under less chronic, but more extreme, conditions, children who have been exposed to severe neglect through institutionalization during the first 6 months of life, show hypersecretion of cortisol to stressful situations in addition to showing emotional and social dysregulation (see above and (Hertzman & Boyce, 2010)). Whether these patterns associated with neglect are due to the absence of early stimulation in general or to the absence of a parent figure is not known. However, HPA function is also associated with how well children are attached to their mothers. Disorganized and insecurely attached children (assessed by how they respond on the 'strange situation test' where the mother leaves the 'strange' experimental room for a short period and then re-enters) show a prolonged HPA stress response to stress situations, whereas securely attached children tend to show a robust but short-lived response (Gunnar, Brodersen, Nachmias, Buss, & Rigatuso, 1996; Nachmias et al., 1996; Rao et al., 2008) (see also Hertzman & Boyce (Hertzman & Boyce, 2010)).

In many of these situations, as reviewed previously, dysregulation of the HPA axis activity is also associated with other behavioural indices of distress, as well as with emotional and cognitive problems, especially in later adolescent years and adulthood. A recent series of studies showed that mothers who were either at-risk teens or clinically depressed were more likely to show less affectionate and disrupted interactions with their babies as well as demonstrating elevated basal cortisol levels (Gonzalez et al., 2012; Krpan et al., 2005). Teen mothers with this endocrine and behavioural profile were also more likely to report (retrospectively), having experienced inconsistent care and multiple and changing caregivers (Krpan et al., 2005). In addition, adult mothers with to early adverse experiences (inconsistent care and/or maltreatment) showed higher levels of diurnal cortisol and were less sensitive when interacting with their infants (Gonzalez et al., 2012).

Taken together, these studies suggest that HPA dysfunction is associated both with concurrent stress and with earlier life stress or adversity and in addition, that these dysregulations have been

associated with mothers' sensitivity and interaction patterns with their infants. Still elusive is whether the elevated cortisol levels in high-risk mothers are particularly related to the postpartum period or were present throughout childhood and generally in adulthood. In fact, several retrospective studies have shown that outside of the postpartum period, women who were abused as children demonstrate elevated peak adrenocorticotropic hormone (ACTH, which stimulates cortisol secretion) responses to stress and a more prolonged cortisol responses. This pattern is strongly associated with a woman's current mood state, such that abused women without current depression demonstrate lower cortisol responsiveness and basal cortisol levels, while women who were abused with depression show features more consistent with hyperactive HPA function (Heim et al., 2004). These data indicate that when interpreting studies using cortisol as a marker for stress, it is important to know the context of the cortisol assessment and the life history and circumstances of the person being assessed. There is also a small literature on fathers' regulation of the emotional and stress response pattern of their children (Mills-Koonce et al., 2011).

d. Early adversity and development of neurochemical and brain function

The animal model has provided a wealth of data indicating that early maternal deprivation affects development of the brain systems important for parenting. To provide only a few examples, work by Champagne and colleagues (Champagne et al., 2004; Numan & Insel, 2003) show that in comparison to offspring of high licking mothers, offspring of low-licking rat mothers grow up to have lower levels of receptors in the brain for the hormones estrogen and oxytocin, and higher levels of receptors on which cortisol acts. These hormones act on receptors in the brain to activate or modulate maternal behaviour. Maternal deprivation studies also show major effects of early deprivation on the development of the brain. Raising rat pups without their mothers, in comparison to mother-reared pups, results in animals that show reduced neural activation in the subcortical brain regions important for mothering (Gonzalez et al., 2001). This is seen in response to pups in juvenile animals raised without their mothers, as well as changes in the dopamine profile in the reward system in the brain (nucleus accumbens) in response to pups in postpartum animals who were not, themselves, mother-raised (Afonso et al., 2011). In both cases, additional touching and stroking stimulation during the early life normalizes brain function and reverses the effects of deprivation. Similarly, early deprivation disrupts normal development of some, but not all, maternal neural circuits by reducing the production of proteins associated with the development of neurons in a number of brain sites important for mothering (Akbari, Chatterjee, Levy, & Fleming, 2007; Burton et al., 2007; Chatterjee-Chakraborty & Chatterjee, 2010; Chatterjee et al., 2007). Finally, there is evidence that many of these effects are initiated during the first week of life in rats, since by day seven of postnatal rearing, maternally deprived animals show reduced normal 'programmed cell death' (called apoptosis) and reduced production of proteins that promote cell death (Chatterjee-Chakraborty & Chatterjee, 2010). It is important to note that, in all these studies, providing additional licking-like stimulation reverses the brain deficits.

In humans, the evidence that early adversity influences the neural underpinnings of later mothering behaviour is less direct. However, some initial data suggested by studies of abused and neglected women and of people raised in the early years in institutions, who have many deficits in brain structure and function, indicate that early adversity may well act on the maternal circuitry. A number of brain changes associated with early life adversity have been reported in

adults, including reduced volume or development of brain areas in the cortex and subcortex (as reviewed in (Teicher et al., 2003). Moreover, in children, the orbitofrontal cortex involved in social-emotional regulation is considerably less active and smaller in maltreated children than in non-maltreated children, and again this reduction is related to the extent of early stress experienced (Bachevalier & Loveland, 2006; Hanson et al., 2010). Similar reduced size has also been reported in institutionalized children; in this case in a portion of the cerebellum that is involved in social regulation, such that children with smaller posterior-superior lobes showed poor executive control (Bauer, Hanson, Pierson, Davidson, & Pollak, 2009; Pollak, 2005; Pollak, 2008).

Adult individuals who experienced early maltreatment report more flatness of affect and depressive symptoms, and display decreased neural activation in reward and learning brain regions compared to non-maltreated counterparts (Buss et al., 2007; Dillon et al., 2009). In a recent study, mothers who reported more nurturing perceived early maternal care had larger grey matter volumes, indicating neuron cell bodies, in many regions of the cortex (Kim et al., 2010). They also exhibited greater brain activation to infant cries in many of the same cortical sites. However, there is a lack of published research examining neurobiological processing in new mothers who themselves have experienced parental loss or personal trauma during early development.

A recent study by Nelson and colleagues (Nelson et al., 2009) found that peer-reared, as compared to mother-reared rhesus monkeys show enhanced responding to an attractive stimulus, in the form of sweet aspartame consumption. In other words, early adversity, in the form of maternal deprivation, is associated with enhanced behavioural responses to reward cues. Nelson et al (Nelson et al., 2009) have suggested that this increased responding to appetitive stimuli may act as a behavioural suppressant for negative emotions, which are often enhanced in animals reared in adverse conditions (Volkow, 2004). That is, early adversity may create inconsistent propensities in offspring; that is, to show a long-term underlying negative emotion bias but also to enhance short-term reactivity to both positive and negative stimuli presented by the environment (see (Lomanowska et al., 2011)). The integrity of the 'maternal brain', its receptor systems and neurotransmitter systems, is essential in both animal models and likely in humans as well, for mothers to respond appropriately to their offspring and create a more nurturing environment for subsequent generations.

6. Genes, gene by environment and epigenetics

How do variations in genes that encode for proteins associated with neurochemicals and hormones known to be important for parenting function to alter maternal behaviour in humans? Do such genomic variants interact with environmental factors in determining individual differences in human mothering? Why are some mothers insensitive/neglectful despite having had a 'stable' and relatively affluent early childhood home environment; whereas others are nevertheless sensitive and attentive mothers despite having experienced considerable adversity? In keeping with our emphasis on neurochemistry associated with the dopamine system, in what follows we restrict our review to only those studies relating to the dopamine system and related pathways that also include the oxytocin genes. These studies suggest that at 6 months postpartum the dopamine and oxytocin neurotransmitter systems are already recruited in the regulation of

maternal behaviour. However, the extent to which these relations persist beyond the early postpartum period, and the role of mediators and moderators in these relations, have yet to be established.

a. Genetics and maternal behaviour

The heritability of maternal behaviour (e.g., positivity, warmth, physical affection, and control) was first indicated by studies with human twins (Kendler & Baker, 2007; Perusse, Neale, Heath, & Eaves, 1994). Recent genetic studies examining the serotonin, dopamine, and oxytocin systems also suggest that maternal genotype predicts maternal behaviours. For example, variation in the DA transporter (DAT1) gene associated with the metabolism of DA is related to differences in the frequency of maternal verbal commands (Lee et al., 2010). In contrast, DA genes that are related to 'less efficient transmission' predict lower maternal sensitivity in mothers with high levels of self-reported daily hassles (Van Ijzendoorn, 2008). When infant fussiness is considered within the context of maternal sensitivity however, mothers with a variant in another dopamine receptor gene (the DRD4 7-repeat allele) behaved more sensitively to fussy babies and less sensitively to non-fussy babies than did mothers with an alternate variant, without the 7-repeat allele (Mileva-Seitz et al., in press).

Our own initial studies relating dopamine genes to mothering at 6 months postpartum focus on two of the dopamine receptor genes, (DRD1 and DRD2 genes)(Mileva-Seitz et al., in press). This study shows that variants in one of these receptor genes (known as the DRD1 single nucleotide polymorphism, SNP) were significantly associated with time mothers spent dis-attending the infant (Mileva-Seitz et al., in press). These findings are consistent with the idea that dopamine acts at this dopamine receptor to enhance the salience and thus attention towards infant stimuli. In contrast, variants within the other type of dopamine receptor gene (DRD2) were significantly associated with maternal vocalizing/speech to the infant. These relations illustrate that different genetic variants can relate to different behavioural endpoints within the mothering system.

In addition, oxytocin genes may also be related to early mothering. A recent study showed that variants at two locations on the oxytocin gene were significantly associated with maternal infant-directed vocalizing at six months postpartum (Mileva-Seitz et al., in press). However, a significant GxE interaction between these gene variations and maternal early life experiences on other measures of maternal behaviour and function (maternal grooming and maternal postpartum depression was also found. These outcomes are similar to results of a recent study that found an interactive effect on mothering of variants in the gene that encodes for the serotonin transporter and early experience (Mileva-Seitz et al., 2011). Finally, consistent with our oxytocin GxE findings, a recent study shows a gene by gene (GxE) interaction, where mothers with one variant in the oxytocin (OT) receptor gene together with one variant in the serotonin transporter gene are less sensitive in their interactions with their infants (Bakermans-Kranenburg et al., 2008). Taken together these studies indicate that mothers differ in their genetic profiles and that mothers with different genetic profiles, may be differentially affected by their environments.

b. Epigenetic mechanisms as they relate to mothering

One intriguing mechanism through which the environment could affect later mothering is gene expression. Such a mechanism has been documented in the cortisol-HPA system of rats (Champagne & Meaney, 2006; Curley et al., 2010; Roth, Lubin, Funk, & Sweatt, 2009; Roth & Sweatt, 2010), and is discussed extensively in Chapter 3. The studies described in Chapter 3 demonstrate the statistical interactive associations of environment and genetic polymorphisms (DNA variations in a single gene) with developmental outcomes, and the molecular epigenetic mechanism through which such interaction could occur. Unfortunately, to date we have no confirmation that epigenetic processes operate on the dopamine or serotonin genes that have been associated with mothering.

Such effects, however, have been found for other gene products that affect mothering, especially for some of the steroid receptors. Steroid receptors are proteins that reside on cells and act to bind steroid hormones, like estrogen and cortisol. Through such binding, the receptor undergoes alterations and the affected neurons become activated. As described earlier, in contrast to high-licking mother rats, mothers who "neglect" their pups are more likely to have female offspring who as adults also lick their offspring less (Champagne et al., 2003; Francis et al., 1999). In the medial pre-optic area (the area of the brain crucial to mothering) these female offspring of low-licking mothers, show both reduced expression of the estrogen alpha receptor gene (and hence are less sensitive to estrogen action), as well as an increased DNA methylation of its promoter region, which functionally reduces or silences gene expression (Champagne & Meaney, 2006). A similar epigenetic process may also affect the BDNF gene, a gene involved in growth and plasticity in the brain, under adverse early experiences (Roth & Sweatt, 2010). Reduction or silencing of gene expression (retention of methylation) is a biological mechanism through which an early adverse experience, as opposed to a positive and healthy experience, could have a long-term impact on processes underlying mothering behaviour. Finally, as early adversity was associated with coherent methylation patterns in the human (postmortem) brains (McGowan et al., 2009), it will be important to document whether the 'gene by early experience' interactions reported in relation to mothering involve differential methylation patterns of the relevant dopamine and serotonin genes.

7. Summary and conclusions

The goal of this chapter was to describe the psychological and physiological mechanisms that regulate parenting, as well as those that account for the intergenerational continuity in parenting. Consistent with the general emphasis on early adversity of the report, the review focused mainly on parental deprivation and adversity. A few points deserve to be highlighted again in concluding this section.

1. **Children who grow up neglected or abused by their parents, or under conditions of extreme distress within their families are at risk of developing a host of unhealthy behaviours that affect their own lives.**

2. **When these children grow up, they tend to be less equipped to take on a parenting role and, in the context of adverse circumstances and the absence of some form of**

social support and/or intervention, they are more likely to adopt inappropriate parenting behaviours and perpetuate a cycle of negative and adverse parenting across generations.

3. **However, despite the probabilistic associations between early adversity and later emotional and parenting problems, most parents who experienced extreme adversity, such as physical abuse, will <u>not</u> adopt the same pattern with their child**. Personal factors, such as temperament, and environmental factors, such as social support to the parent or to the developing child, from the partner, the family, and the community mitigate the risk of inappropriate parenting.

4. **Mothers who are depressed, reactive, inattentive, impulsive, aggressive, or who are simply not interested in their children are more likely to adopt inappropriate parenting behaviours, especially in stressful situations.** The perceptual, cognitive, and emotional deficits that many mothers experience affects their children in different ways; for instance, as we have discussed, if untreated, depressed mothers can put their children at risk for depression and other affect problems, whereas children who are physically abused or the target of harsh parenting may come to show externalizing behaviour and harsh parenting themselves. Neglectful parenting, inconsistent parenting or insensitive parenting may be differently regulated and, in turn, produce problems in the child's own attachments and later relationships.

5. **The underlying mechanisms linking early adversity and later parenting difficulties imply a disruption of behavioural and physiological processes usually involved in normal parenting, including stress regulation.**

6. **Studies relating mothers' depression and difficult parenting to child outcomes indicate the importance of environmentally mediated influences, over and above a genetic liability for poor outcomes shared by parents and children.** Research is now weighing on the possible biosocial processes, such as gene-environment transactions and epigenetic processes, reviewed in the previous chapters, accounting for this continuity in parenting across generations.

7. **The extant research suggests that, in addition to policies at a societal level (aimed at reducing poverty and drug abuse, and improving education) and interventions specifically directed at the child, we also need to consider interventions that focus on parenting difficulties.** In so doing, both mothers and fathers' mood states and emotion regulation need to be considered. Some of these programs exist and have proven to be effective (see the chapter on intervention). However, more interventions directed specifically at helping parents parent more effectively should be evaluated using the same high standards of effectiveness. Among the current approaches to interventions, we should also be considering programs aimed at enhancing parents' emotion regulation and impulse control, attentional and cognitive capacity, mood state, ability to cope with stress, and more specifically in the context of parent-child interaction; i.e., attention to infant signals, contingent responding and positive regard. Only by understanding the phenomenology of parenting, its precursors and consequences, and its underlying

mechanisms, will we be in a position to attend to the needs of the parents, to enhance their overall well-being and to help them gain the tools to more effectively attend to the needs of their children.

CHAPTER FIVE: CHILD MALTREATMENT. INTERVENTIONS TO PREVENT CHILD MALTREATMENT AND ASSOCIATED IMPAIRMENT IN CHILDHOOD AND ADOLESCENCE

1. Introduction

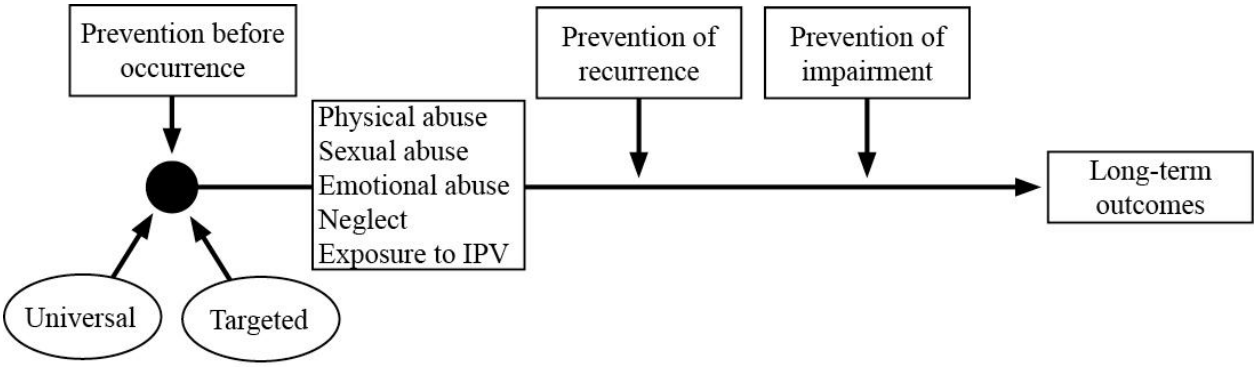
As outlined in earlier chapters, there is a broad range of adverse experiences in early development to which children can be exposed including poverty, parental use of banned substances and child maltreatment, among others. A review of interventions to reduce exposure to all childhood adversities and to the associated impairments is beyond the scope of this chapter. However, we do provide an overview of the interventions aimed at preventing one of the most pervasive and serious adversities—child maltreatment—as well as associated impairments. We hope the approach to considering the evidence supporting interventions to prevent child maltreatment and its associated consequences, outlined below can be applied to other adversities such as parental mood disorder.

As discussed in earlier chapters, there can be considerable overlap in children's exposure to early adverse experiences, and these overlapping experiences can lead to significant *cumulative* risk. Similarly, some interventions have the potential to address more than one childhood adversity. Interventions are often developed on the basis of identified "risk factors," that is, factors that are significantly related to one or more outcomes (such as child maltreatment). Of identified risk factors, some can be determined to be "causal risk factors;" that is, risk factors that are changeable and can be manipulated such that, when successfully manipulated, the risk of the negative outcome occurring is reduced (Kraemer et al., 1997). Identification of such causal risk factors is important in developing effective prevention programs. A second prevention challenge is to understand the specific mechanisms by which an adversity—once it occurs—leads to impairment. If these mechanisms can be identified, it may be possible to intervene before the sequelae occur. Earlier chapters have highlighted that the field has made headway in identifying specific causal risk factors and that much is known about the correlates of impairment. However, there remains a need for much greater investment in determining how such knowledge can be applied to the development of interventions.

The impairments in the development of children associated with exposure to child maltreatment are now widely recognized. This chapter reviews the current evidence about approaches to preventing one or more of the five major subtypes of child maltreatment: physical abuse, sexual abuse, emotional abuse, neglect and exposure to intimate partner violence (IPV), and to preventing the impairments associated with these experiences. In addressing this topic, we follow the framework adapted from a recent review of child maltreatment preventions ((MacMillan et al., 2009); see Figure 5.1). We include interventions aimed at (1) preventing maltreatment before it occurs; and (2) preventing repeat maltreatment (recidivism) and reducing adverse outcomes associated with maltreatment among children and adolescents. "Interventions" include any program or strategy aimed at preventing child maltreatment or associated impairments. While it can be difficult, at times, to ascertain the onset of maltreatment and thereby separate out prevention of maltreatment from its recurrence, programs typically identify one or the other as a focus. We have categorized them according to their stated intervention goal. We have deliberately avoided use of the terms "primary, secondary and tertiary" prevention, because of

the confusion that often arises with their application to the child maltreatment field. For example, the World Health Organization uses primary prevention to refer to any type of intervention aimed at stopping maltreatment before it occurs, whether administered universally or to a group considered at high risk (or selected) (Mikton & Butchart, 2009), whereas others use primary prevention to infer a focus on the general population, and secondary prevention to infer a focus on families with risk factors associated with maltreatment (Child Welfare Information Gateway).

The chapter provides an evidence-based overview of what we know from the peer-reviewed literature about the effectiveness of specific interventions in reducing child maltreatment and associated impairment. We have focused on high-quality literature syntheses and studies of interventions with control groups, notably randomized controlled trials (RCTs) when available. Our aim has been to include studies of interventions that specifically address reduction of child maltreatment and/or associated objective outcomes such as injuries, as well as impairment. Selection of which outcomes are "primary" and which are "secondary" for purposes of determining the effectiveness of a program is a critical methodological issue (MacMillan et al., 2009). For example, official case reports of maltreatment are well recognized for underestimating exposure to child maltreatment (Theodore et al., 2005). Similarly, caregiver self-reports of harmful behaviour directed toward a child are potentially subject to underreporting because of awareness that such behaviours are not socially acceptable (the "social desirability" bias). Despite evidence supporting the validity of children's self-reports of victimization (Finkelhor, Ormrod, Turner, & Hamby, 2005), much maltreatment is experienced by children too young to self-report. Given these (and other) limitations that are inherent in the identification of occurrence of maltreatment (Runyan, 2008), wherever possible we focus on those studies that have used objective measures of child and caregiver behaviours and exposure to maltreatment.



[1]Adapted from MacMillan et al. Lancet 2009

Figure 5.1. *Framework for review of child maltreatment prevention interventions.*

The reader is also referred to a systematic review of reviews by (Mikton & Butchart, 2009) that synthesizes evidence for the effectiveness of the main categories of interventions for preventing child maltreatment, such as home visiting and parent education, among others. The latter review focuses on broad types of interventions, whereas this chapter discusses the effectiveness of individual programs.

2. Prevention before occurrence of maltreatment

a. Physical abuse and neglect

Despite evidence that there are important epidemiologic differences between physical abuse and neglect (English et al., 2005), reduction of these two subtypes of child maltreatment is a combined focus in many prevention programs (MacMillan et al., 2009), and so we consider them together.

Systematic reviews of programs aimed at prevention of child physical abuse and neglect have yielded mixed results (Barlow, Simkiss, & Stewart-Brown, 2006). MacMillan et al. (MacMillan, MacMillan, Offord, Griffith, & MacMillan, 1994) assessed six interventions reported in 11 studies: 1) home visitation (six studies) (Barth, 1991; Hardy & Streett, 1989; Larson, 1980; Olds, Henderson, Chamberlin, & Tatelbaum, 1986; Siegel, Bauman, Schaefer, Saunders, & Ingram, 1980; Taylor & Beauchamp, 1988); 2) parent-training (Resnick, 1985; Wolfe, Edwards, Manion, & Koverola, 1988); 3) intensive contact with a pediatrician coupled with home visitation (Gray, Cutler, Dean, & Kempe, 1979); 4) early and/or extended postpartum hospital-based contact alone or combined with home visits (O'Connor, Vietze, Sherrod, Sandler, & Altemeier, 1980; Siegel et al., 1980); 5) use of a drop-in centre (Lealman, Phillips, Haigh, Stone, & Ord-Smith, 1983) and 6) free transportation for prenatal and well-child care (Olds et al., 1986). Evaluation was restricted to outcomes defined by official reports of suspected or verified abuse and neglect as well as three "proxy" measures (hospitalizations, emergency visits, and injury rates). The reviewers concluded that there was insufficient evidence supporting the effectiveness of any of the interventions in preventing physical abuse and neglect other than home visitation. "Home visitation" programs were not all identical with each other, and the evidence for home visitation effectiveness was mixed across the six studies. The most rigorous study of one home visitation program showed positive results for the prevention of child maltreatment and associated outcomes such as injuries (see below; (Olds et al., 1986)). This program has subsequently undergone a much longer follow-up and two replications (further details below).

An update to the 1994 review by MacMillan et al (MacMillan, 2000) identified two additional types of interventions: 1) a combination of home-based services that included case management, education and psychotherapy (Huxley & Warner, 1993); and 2) provision of comprehensive health services that included prenatal, postnatal and pediatric care provided in a clinic setting (Brayden, Maclean, Bonfiglio, & Altemeier, 1993). Also, an additional parent-training program had become available (Britner & Reppucci, 1997). However, the review concluded that the evidence that any of these three programs were effective in preventing maltreatment was still insufficient.

In a second review, MacLeod and Nelson (MacLeod & Nelson, 2000) conducted a meta-analysis of programs aimed both at prevention of child maltreatment and at promotion of family wellness. Using a measure of "effect size" (d) (that is, a measure of the proportion of those in treatment who improve, compared to the untreated controls) that permits comparisons of effectiveness of programs using different outcomes across studies, the authors reported that the most effective preventive interventions with medium effect sizes were "multi-component" (d = .56) and home visitation (d = .41) programs. However, their conclusions were difficult to interpret because they

combined results across a very broad range of interventions and outcomes, and it was not clear if individual study quality was taken into account when combining the results.

Geeraert and colleagues (Geeraert, Van den Noortgate, Grietens, & al., 2004) conducted a meta-analysis of mixed study designs (that is, studies that included uncontrolled evaluations) of programs for families with children up to age three years. They did not evaluate individual study quality. Most of the interventions included were home visitation programs; others were hospital- or clinic-based programs. The authors concluded that the effect size for these programs was modest (d = .29), based on combining effect sizes across a range of outcomes (reports of abuse, parent and child functioning, parent-child interactions, among others).

i. Home visitation

As suggested previously, the phrase "home visiting programs" does not always refer to a uniform intervention. Home visitation programs may vary widely in regard to services delivered, content, and/or staffing (Kamerman & Kahn, 1993). Although a wide range of early home visiting programs to prevent child maltreatment have been promoted (American Academy of Pediatrics & Council on Child Adolescent Health, 1998; Bull, McCormick, Swann, & Mulvihill, 2004), most have not been shown to reduce physical abuse and neglect when evaluated by randomized controlled trials (RCTs; (Olds, Sadler, & Kitzman, 2007b)). Although some systematic reviews and meta-analyses reached the general conclusion that early childhood home visitation is effective in preventing child abuse and neglect (Bilukha et al., 2005; MacLeod & Nelson, 2000), these evaluations have not generally considered the substantial variability across programs (Gomby, 2000). When considering the evidence for prevention of physical abuse and neglect using objective outcomes such as child hospitalizations, emergency visits, and injury rates, only two home visiting programs have shown significant benefits. These are the Nurse-Family Partnership (NFP) developed in the USA and the Early Start Program developed in New Zealand.

1. Nurse-Family Partnership

The NFP is an intensive home visitation program delivered to low-income first-time mothers by nurses beginning prenatally and extending to the end of the child's second year (see Textbox 5.1;(Olds et al., 2007a)). It has been evaluated in three RCTs across a range of samples and locations in the USA: Elmira, New York; Memphis, Tennessee; and Denver, Colorado. The third and most recent trial (Denver) included a comparison arm in which the intervention was delivered by paraprofessionals (Olds et al., 2002). Each of the trial samples continues to be followed for evaluation of long-term outcomes. Unfortunately, it has not always been possible to measure the same outcomes consistently across trials. For example, in the Memphis trial, the rate of verified child abuse and neglect among two-year old children was too low to serve as a valid measure of child maltreatment

During the first two years of the child's life, nurse-visited children born to a high-risk subgroup of the Elmira trial sample—single, low-income adolescent mothers—showed a reduction in the number of verified cases of child abuse and neglect that almost reached criteria for being statistically significant (Olds et al., 1986). Although this effect was not apparent during the follow-up two years after the program ended, in the whole sample of mothers, child maltreatment

was identified less often in the nurse-visited group compared with the control group by the time the children were 15 years of age (Olds et al., 1997). In the two trials where it was possible to measure injuries (Elmira and Memphis), there was a statistically significant reduction in health-care encounters for injuries and ingestions when the child was two years of age (Kitzman et al., 1997; Olds et al., 1986). A review of the nature of the childhood injuries experienced by children in the intervention versus the control arms of the Memphis trial indicate a strong association with child maltreatment for many of the injuries. These include conditions unlikely to have been the results of unintentional accidents, such as fractured fibula in an infant less than three months, bilateral subdural hematoma in two infants less than six months and burns in an infant less than four months, among others.

As results have become available about the long-term outcomes among nurse-visited children compared with controls, there is evidence for reduction in the forms of child neurodevelopmental impairment that have been shown to be associated with child maltreatment. Nurse-visited children did not show significant differences in cognitive development at age four years in the Elmira trial, but all nurse-visited children in Memphis and Denver displayed significantly better language development at ages two and six years (Olds et al., 2002; Olds et al., 2004). Language development is not itself a specific indicator of child maltreatment, but there is an association between exposure to one or more types of child abuse or neglect and delayed language acquisition (Eigsti & Cicchetti, 2004).

Similarly, enduring effects have been shown for a reduction in antisocial behaviour among nurse-visited children from the Elmira trial at both 15 and 19 years of age, although the latter effect was concentrated in girls (Eckenrode et al., 2010; Olds et al., 1998). There are mixed findings for improvements in anxiety and depressive symptoms, with improvements at age 12 in Memphis (Kitzman et al., 2010), but not at age 15 in Elmira (Olds et al., 1998).

Although the NFP is a nurse home visitation model, the Denver trial also examined the effectiveness of home visitation delivered by paraprofessionals compared with nurses and a control group (Olds et al., 2002). The visitors had personal attributes and knowledge of the community, and (by design) no training at the college level (Olds et al., 2004). Visits by paraprofessionals did lead to some improvements for mothers, but they did not improve children's outcomes and the effects were not as strong as those seen with nurse home visitors, across a wide range of outcomes. Following the Denver trial, the investigators concluded that further trials with paraprofessionals could not be justified.

In addition to the benefits of the NFP identified above in preventing child maltreatment and associated outcomes, an analysis conducted by the Washington State Institute for Public Policy estimated that for every family served by the NFP, society receives an approximately $17,000 return on the investment (Aos, Lieb, Mayfield, Miller, & Pennucci, 2004)

As of early 2011, the NFP has been implemented in 32 states in the USA and is being evaluated in the United Kingdom and the Netherlands; in addition, there is a pilot study underway in Canada to determine if the benefits identified in the three USA trials can be replicated. Other modifications to the NFP are under investigation. For example, in the Elmira trial, the reduction in child maltreatment when the child was 15 years of age were not seen when there were high

levels of intimate partner violence (IPV) in the home, although the other benefits remained. A curriculum enhancement specific to reducing IPV has been developed for the NFP and will be evaluated in a randomized controlled trial comparing the existing NFP model with an intervention that includes the IPV curriculum augmentation.

2. The Early Start Program

This intensive home visiting program developed in New Zealand targeted high-risk families and begins post-natal (see Textbox 5.2). Eligible families were referred based on a screening procedure that included questions about parenting and family functioning, as well as those about whom nurses had serious concerns regarding their parenting capacity. The intervention was delivered by nurses or social workers. In a randomized controlled trial comparing families assigned to the Early Start program with a control group of families not receiving the intervention, home-visited children had significantly lower attendance at hospital for childhood injuries and fewer hospital admissions for severe maltreatment at follow-up after three years (Fergusson et al., 2005a). Reports of physical abuse by parents in the intervention group were also reduced. Rates of referrals to official child protection agencies for care did not differ between the groups. This was attributed to a surveillance bias, whereby the clients receiving the home visits were subject to greater scrutiny than the controls.

3. Paraprofessional models

In comparison to the two programs discussed above, most of the home visitation studies evaluating effectiveness for preventing physical abuse and neglect have focused on models in which the service is delivered by paraprofessionals (Geeraert et al., 2004). The two that have undergone the most extensive evaluations have been the Hawaii Healthy Start Program (HSP) and Healthy Families America (HFA; based on HSP) (Duggan et al., 2007; Duggan et al., 2004; Duggan et al., 1999). The Healthy Start Program served as the basis for the subsequent Healthy Families America program. Both programs have been evaluated with randomized designs. However, the intervention was disseminated to other implementation sites based on the results of the earlier, less rigorous, studies. In a follow-up of the original Healthy Start Program, there were few effects on outcomes such as hospitalizations for trauma, verified child protection reports or parental reports of abusive caregiving. Mothers in the Healthy Start Program were less likely to self-report neglectful behaviours on a revised Conflict Tactics Scales (CTS) subscale, but the traditional CTS approach to measuring neglect showed no effect of the intervention. Subsequent follow-ups of the derived Health Families America randomized controlled trials in Alaska and San Diego showed few or no effects, respectively (Duggan et al., 2007; Landsverk et al., 2002).

Two-year findings from a New York Healthy Families America trial showed no differences between groups in either occurrence or frequency of verified child protection records or the occurrence of abusive or neglectful behaviours reported by mothers (Caldera et al., 2007). There were some benefits in maternal self-reported outcomes, such as fewer acts of very serious physical abuse, minor physical aggression and psychological aggression at one-year follow-up. However, when one takes account of the fact that these few positive results emerged from more than 14 outcomes and that they were all self-reports by the mother, their value remains questionable.

ii. Parent-training programs

A number of parent-training programs are being used with the stated goal of preventing child maltreatment (Krugman, Lane, & Walsh, 2007), but only the Triple P program has been evaluated for its effectiveness by using actual child maltreatment outcomes. One trial examined the effectiveness of the Triple P program to prevent child abuse and neglect in a community-based study in which 18 counties within a southeastern state in the USA were randomly assigned to an intervention or a control group (that is, services as usual) (Prinz, Sanders, Shapiro, Whitaker, & Lutzker, 2009). It involved the implementation of professional training for the workforce, in addition to universal media and communication strategies addressing positive parenting strategies, as the first level of a multilevel system that included five intervention categories of increasing intensity (see Textbox 5.3). Three population-level indicators were used to determine intervention effectiveness: rates of verified child maltreatment; out-of-home placement; and hospitalizations or emergency room visits for child maltreatment injuries. Positive effects in the counties that implemented the Triple P program were found for all three indicators. However, it is important to note that the effect sizes reported were between-cluster differences rather than individual differences. This means that we cannot be sure that these community-level results apply to the individual. Furthermore, information that would have been helpful in interpreting the results of the statistical analyses, such as standard deviations, was not provided. The authors state that this population trial was based on "a large body of evidence" that includes intervention fidelity, thereby justifying the lack of individual-level data (Prinz et al., 2009). However, previous clinical trials did not asses—nor was the intervention aimed at—prevention of child maltreatment. This intervention shows promise, however, so it would be important for a future replication to include individual-level data.

iii. Abusive head trauma education programs

Abusive head trauma (AHT, also known as shaken baby syndrome [SBS];(Christian & Block, 2009)) is a distinctive form of infant abuse in that it is increasingly clear that there is a specific stimulus (crying) and a specific risk factor (shaking) that results in the abuse. Because the increased crying is a reflection of normal behavioural development (Barr, Trent, & Cross, 2006; Lee, Barr, Catherine, & Wicks, 2007; Talvik, Alexander, & Talvik, 2008) and AHT/SBS occurs primarily within the first six months, prevention has focused on targeting education to caregivers during the newborn period, as a primary caregiver universal prevention program. This strategy differs from other prevention programs in targeting the whole population of parents of newborns rather than just "at risk" groups.

The first such program was developed and evaluated by Dias and colleagues (Dias et al., 2005). The core concept is that delivering prevention materials during the immediate postpartum period exploited a "teachable moment" that would make the intervention most effective if delivered by nurses. The intervention was provided by nurses to parents on the postpartum ward in 16 hospitals in western New York State. It consisted of providing a one-page educational leaflet and posters, showing a brief video, and having parents sign a 'commitment statement' that they had received the materials. The materials focused on the dangers of violent infant shaking and on suggestions about how to handle persistent crying. The incidence of abusive head injuries in children less than 36 months of age was tracked prospectively for 66 months and compared with

the incidence in the previous 66 months. The incidence of AHT identified following introduction of the program (22.2 cases per 100,000 births) represented a significant reduction relative to the incidence prior to the study period (41.5 cases per 100,000 births). A similar program introduced in Utah between 2001 and 2007 using videos, written materials, posters and magnets with a "don't shake" message was evaluated in an observational case control study (Keenan & Leventhal, 2010). Although there was a decreased risk of AHT occurrence similar in size to the New York program, the study design did not support a causal connection of AHT cases with exposure to the program.

The encouraging results from the Dias study have stimulated additional efforts to prevent AHT/SBS, taking account of previous limitations in materials and methods of distribution. New materials have been designed and tested that reflect evidence supporting positive teaching materials (Russell, Trudeau, & Britner, 2008). In two randomized trials, a DVD and booklet from the National Center on Shaken Baby Syndrome (NCSBS) in the USA, focusing on improving understanding of normal crying in the first months of life, has been shown to increase knowledge and some behaviours relevant to preventing SBS (Barr et al., 2009a; Barr et al., 2009b). Current trials include an attempted replication by Dias and colleagues in every hospital in Pennsylvania with the addition of reminder messages in approximately one-third of pediatric practices in the state. In British Columbia, Canada, and in North Carolina, USA, jurisdiction-wide trials of the NCSBS materials have been implemented as part of a comprehensive "three dose" program that includes delivery of education at the birth of the baby, reinforcement before and/or after delivery, and public education directed to society at large. Outcomes will include incidence of AHT/SBS hospitalizations and deaths, effects on emergency room visits and after-hours nurse-line calls, and changes in knowledge and behaviours of the general public.

iv. Enhanced pediatric care for families at risk

Dubowitz et al. (Dubowitz, Feigelman, Lane, & Kim, 2009) examined the efficacy of the Safe Environment for Every Kid (SEEK) model of pediatric primary care in a university-based, pediatric resident, continuity clinic serving primarily a low income urban community of single mothers in Baltimore, Maryland. Clinics were randomized to receive routine pediatric care provided by the pediatric residents (250 families) or Model care (308 families). In Model care, residents received special training, used the Parent Screening Questionnaire to identify family problems, and had a social worker available for referral. Prior to the intervention, 12% of families in each group had been reported to Child Protective Services (CPS). During the intervention, there were fewer CPS reports in the Model care group (13.3%) than in the routine care group (19.2%) ($p=0.045$ [one-tailed]). In addition, there were fewer problems related to possible medical neglect (non-adherence to medical care [4.6% vs. 8.4% $P = 0.05$] and delayed immunizations [3.3% vs. 9.6%; $P = 0.002$]) and fewer severe or very severe physical assaults reported by parents ($P = 0.04$). The results suggested that enhancing primary care physicians' abilities to identify risks and help families decrease risk factors for child maltreatment may be effective; however, further evaluation, especially with pediatricians in private practice settings, is needed.

b. Sexual abuse

Education programs have been the main approach to preventing sexual abuse (Davis & Gidycz, 2000; Zwi et al., 2007). Systematic reviews conducted since 1994 (Davis & Gidycz, 2000; MacMillan et al., 1994; Rispens, Aleman, & Goudena, 1997; Zwi et al., 2007) have examined an increasing number of randomized controlled trials evaluating universal school-based programs. In the most recent systematic review, Zwi and colleagues (2007) considered the evidence from 15 trials that examined the effectiveness of school-based curricula for children from kindergarten through to high school, primarily in the USA. The programs involved combinations of film/video, discussion and role-play that varied in session duration from fewer than 90 minutes to a cumulative maximum of about five and a half hours. Most commonly, the control groups were children randomly assigned to the wait list or those who received the standard curriculum; in a minority of studies, control subjects received a program with no child abuse content. A significant improvement in measures of knowledge was reported in most studies; a smaller proportion that evaluated protective behaviours (e.g. running away from a stranger) under simulated conditions found significant gains in this area as well. Only three studies measured disclosures of past or current sexual abuse. Because of methodological limitations, such use of quasi-experimental design in one study and failure to distinguish disclosures from the control versus experimental group in another, it was not possible to determine whether such disclosures were affected by the intervention. Three studies reported unfavourable outcomes such as increased anxiety. Many of the studies suffered from major methodological weaknesses that included absence of blinding, analyses that failed to take into consideration cluster randomization, and follow-up that was very short, typically for only three months following the end of the program. In their review, Zwi and colleagues (2007) reached the same conclusions as did three earlier systematic reviews (Davis & Gidycz, 2000; MacMillan et al., 1994; Rispens et al., 1997); namely, that it is still unknown whether increased knowledge and use of protective behaviours translate into reduced sexual abuse. Therefore, it remains unknown whether education programs aimed at children actually prevent sexual abuse (Zwi et al., 2007).

c. Emotional abuse

Despite increased awareness of the associated impairments, emotional abuse among children is an exposure that is neither well-defined nor understood (Glaser, Prior, & Lynch, 2001). One review (Barlow et al., 2008) examined the effectiveness of attempts at the prevention of early indicators of emotional abuse, such as emotional unavailability (as defined by (Glaser, 2002)). Barlow and colleagues (2008) provided the following summary. Several studies have evaluated interventions such as parent-infant psychotherapy or home-visiting programs aimed at reducing risk factors for emotional abuse, such as maternal insensitivity. These have been summarized in a meta-analysis of attachment-based interventions (Bakermans-Kranenburg, van Ijzendoorn, & Juffer, 2003). Results from randomized controlled trials have demonstrated reductions in insensitive parenting and in infant attachment insecurity. Maternal insensitivity is an important element predisposing to emotionally harmful parent-child relations, but it is only one indicator of potential emotional abuse, underscoring the challenges of developing interventions to prevent emotional abuse generally.

d. Exposure to Intimate Partner Violence (IPV)

Clearly, efforts that reduce the occurrence of intimate partner violence (IPV) will prevent exposure to this negative early life event for children. Primary prevention of IPV through educational programs has focused on changes in knowledge and attitudes rather than actual reduction in IPV. In one study of adolescent dating violence (considered a precursor to IPV in adulthood), an interactive curriculum for Grade 9 students that included information about dating violence and healthy relationships was associated with a statistically significant reduction in self-reported physical dating violence, but the differences were small (Wolfe et al., 2009). Generally, however, two systematic reviews highlight the paucity of evidence for effective interventions to prevent the occurrence of IPV (Nelson, Nygren, McInerney, & Klein, 2004; Wathen & MacMillan, 2003).

There is promising evidence that an advocacy/empowerment program provided through postnatal clinics might reduce psychological and minor physical violence, based on results of a randomized controlled trial conducted in China (Tiwari et al., 2005). In a USA trial of a brief counseling intervention provided during pregnancy, there was a reduction of violence and improved pregnancy outcomes (Kiely, El-Mohandes, El-Khorazaty, & Gantz, 2010). Outside of health care settings, intensive advocacy may have reduced physical abuse among women leaving shelters for the first two years, but by three years the benefits had disappeared (Bybee & Sullivan, 2005).

3. Prevention of recurrence and impairment

In conceptualizing responses to the occurrence of child maltreatment, it is important to highlight that maltreatment is an exposure; it is not itself a symptom or a disorder. Preventing recurrence of maltreatment and impairment from the occurrence of maltreatment are related goals, but they are not necessarily achieved with the same interventions.

Prevention of recurrence typically focuses on reducing the abusive or neglectful behaviours of adults, often within the context of parenting. This section includes those programs or approaches specifically directed at reduction of maltreatment recurrence within the context of the parent-child relationship. Other interventions, such as programs aimed at child molesters, are beyond the scope of this chapter.

Since out-of-home care is a general intervention that can be considered in relation to all types of maltreatment and their associated impairments, it is discussed separately below. One meta-analysis (Skowron & Reinemann, 2005) evaluated the effectiveness of psychological treatments for all categories of maltreatment. They concluded that there was an overall positive effect, although when self-report outcomes were excluded, the size of this effect was reduced. Given the heterogeneous nature of interventions considered in this meta-analysis, it was not possible to determine the specific effectiveness of these programs.

a. Physical abuse and neglect

i. Programs for parents/families

1. Parent-training programs

Only one recent review has focused specifically on the effectiveness of parent-training programs to prevent the recurrence of physical abuse or neglect (Barlow et al., 2006). It included seven randomized controlled trials that targeted parents with a history of child physical abuse (five studies), physical abuse and neglect (one study) or unspecified abuse (one study). Of these studies, three included a control group and four used an alternative treatment (comparison) group. Only three of the studies examined the impact of parent-training on objective measures of recurrence such as reports by child protective workers (Wolfe, Sandler, & Kaufman, 1981), number of injuries (Kolko, 1996), or official re-reports of physical abuse and neglect (Chaffin et al., 2004).

A study (Chaffin et al., 2004) of parent-child interaction therapy (PCIT; see Textbox 5.4) compared the effectiveness of PCIT alone and PCIT plus individualized *enhanced* services (*E*PCIT) with a standard community-group psycho-educational (didactic) program (n = 110). At follow-up, there was a reduction in re-reports of physical abuse among the parents in the PCIT condition compared with the control and EPCIT groups, but no difference in re-reports of neglect.

The second study randomly assigned 38 physically abused children and their families to either cognitive behavioural therapy (CBT) or an ecologically-based family therapy (FT) program focused on family interaction (Kolko, 1996). Both services included 12 one-hour weekly clinic sessions with follow-up home sessions to evaluate progress. There were significantly fewer child reports and parental reports of physical discipline/force in the CBT group compared with the FT group. The number of injuries was too small to permit a statistical comparison (Kolko, 1996).

The third study evaluated the effectiveness of a group-based parenting program of instruction in child management techniques, problem-solving and modeling of appropriate child management (Wolfe et al., 1981). At one-year follow-up, the reports of abuse across the groups were too few to conduct reliable comparisons. Furthermore, there was no difference between groups in caseworker ratings of family treatment needs post-intervention.

An important limitation of these efforts is that most studies provide immediate post-intervention assessment only (Barlow, Parsons, & Stewart-Brown, 2005). Barlow and colleagues (2005) found limited evidence to support the use of parent-training program to reduce the recurrence of physical abuse; however, PCIT did result in reduced reports of physical abuse. It was surprising and counterintuitive that *enhanced* PCIT resulted in poorer outcomes than the general PCIT model.

A more recent trial evaluated the effectiveness of PCIT compared with an "attention only" wait-list control group provided to mothers with a history of, or at high risk of, maltreating their children (Thomas & Zimmer-Gembeck, 2007). Data were gathered from official child protection

records. Since the "attention only" group was offered treatment after completion of the wait-list, it was not possible to compare reports between groups. Since this trial did not include any comparisons of objective measures, it was not considered an actual replication of the trial by Chaffin and colleagues (Chaffin et al., 2004). There is also limited evidence to suggest that some types of parenting programs (e.g., Webster-Stratton Incredible Years Program: (Hughes & Gottlieb, 2004)) may be effective in improving outcomes that are associated with physically abusive parenting including, for example, child reports of parental anger (Kolko, 1996).

2. Home visitation and in-home programs to prevent recurrence of child maltreatment

A randomized controlled trial evaluated a program of home visiting by nurses provided to families involved with the child protection system (MacMillan et al., 2005). Families with at least one child aged newborn to 12 years who had experienced physical abuse or neglect were randomly assigned to a two-year intervention of nurse home visitation coupled with standard care provided by child protection workers or standard care alone. Although theoretically based on the NFP, it involved a different sample of families already involved with child protection, and a different program and outcomes. At the three-year follow-up, there was no difference between groups in incidents of physical abuse or neglect; nor was there any indication that associated outcomes such as injuries had been reduced. Nurse-visited families involved with the child protection system for fewer than three months had a reduction in physical abuse but not neglect; however, this finding was not anticipated prior to the study, and may be a chance finding.

SafeCare is an in-home behavioural skills training program originally developed for parents involved with child protection services (CPS) for neglect ((Chaffin, Hecht, Bard, Silovsky, & Beasley, 2012); see Textbox 5.5). It is based on Project-12-Ways, an earlier, multi-faceted, in-home program that was condensed to a 24-week intervention with parent training around three main components: basic caregiving, household management and parenting skills. The SafeCare model was reported in a "completers-only" trial to reduce the recurrence of physical abuse and neglect when compared with a family preservation program (home-based program providing intensive support services) (Gershater-Molko, Lutzker, & Sherman, 2002; Gershater-Molko, Lutzker, & Wesch, 2003). However, major limitations in study design and methodologic weaknesses precluded drawing conclusions about SafeCare's effectiveness in reducing recidivism based on this earlier trial. More recently, a state-wide trial involving a 2 x 2 cluster experimental design tested SafeCare versus home-based services as usual (SAU) and coached versus uncoached quality control strategies in reducing CPS recidivism (Chaffin et al., 2012). Analyses of recidivism outcomes showed that the SafeCare model was effective; main effects were significant with hazard ratios (HRs) between 0.74 and 0.83, while the coaching strategy showed smaller and less consistent benefits (HRs between 0.85 and 0.94). This trial had some strengths, including its use of CPS data, an average length of follow-up of six years, and that it was evaluated on a scaled-up statewide implementation. An important limitation was that there were a small number of clusters (n = 6). Although this model was originally developed for neglectful parents, eligible participants included all maltreating caregivers referred to the program by CPS other than those referred for sexual abuse. The results suggest that SafeCare is a promising program to reduce recurrence of maltreatment (other than sexual abuse) among those referred to CPS.

3. Programs focused specifically on neglect

Allin et al. (Allin, Wathen, & MacMillan, 2005) conducted a systematic review of studies evaluating interventions specifically designed for child neglect that included control or comparison groups. Few evidence-based treatments were identified, either for children exposed to neglect or for their caregivers. This review found that "resilient peer treatment" (RPT; (Fantuzzo et al., 1996)) improved social interactions and reduced behaviour problems, although the sample size was small and the follow-up was only for two months. A larger study of RPT published after this review (Fantuzzo, Manz, Atkins, & Meyers, 2005) confirmed earlier positive effects for maltreated children when this program was integrated into Head Start classrooms. A program of "imaginative play training" (Udwin, 1983) led to improved peer interactions, more positive affect and better cooperation, however the sample size was very small and follow-up was lacking. Multisystemic therapy that included family sessions in home or clinic focusing on such topics as child management and family interaction reported improved parent-child interactions when compared with a parent-training program; however, the sample size was small, groups were not equivalent on some characteristics and the follow-up occurred just one week post-treatment (Brunk, Henggeler, & Whelan, 1987). A specific therapeutic day treatment program evaluated in a nonrandomised comparison study showed some effect in improving neglected children's self-concept (Culp, Little, Letts, & Lawrence, 1991).

b. Sexual abuse

i. Programs for children and families

Several psychological treatments aimed at reducing impairment associated with sexual abuse have been systematically reviewed (Macdonald, Higgins, & Ramchandani, 2006; Ramchandani & Jones, 2003). Outcomes included internalizing and externalizing symptoms or disorders, and manifestations of sexualized behaviour. The children participating have ranged in age from preschool to 17 years, and some interventions have involved parents in the treatment. Ramchandani and Jones reviewed 12 randomized controlled trials published before December 2002; most assessed individual cognitive behavioural therapy (CBT). Comparisons generally involved either a wait-list control group or a group receiving some other type of supportive therapy. The best evidence was for CBT, particularly for children who had symptoms of posttraumatic stress disorder (PTSD). Studies reporting a positive effect involved a parent or caregiver in the treatment. Improvement was also noted in behavioural problems, including reduced sexualized behaviour. The overall methodologic quality of the studies was low, often because of inadequate description of the methods. Although the majority of children and families improved, some became worse. When individual therapy was compared to group therapy, the evidence regarding effectiveness was considered too inconsistent to reach a conclusion.

The efficacy of CBT for sexually abused children was assessed in a recent review that included randomised or quasi-randomised studies prior to November 2005 (Macdonald et al., 2006). The CBT interventions varied in program content and frequency (six to 20 sessions), but generally included the following themes for the child sessions: safety education, coping skills, cognitive processing of the abusive experience, identification of inappropriate behaviours, relaxation techniques, dealing with problems related to the abuse and graduated exposure in reducing

avoidance behaviour (Macdonald et al., 2006; Stallard, 2006). Parent or joint sessions focused on parent-child communication, psycho-education, cognitive reframing and parent-management training (Macdonald et al., 2006; Stallard, 2006). Results of the meta-analyses indicated decreases in depressive, PTSD and other anxiety symptoms at one year follow-up, but no effect, on average, on sexualized behaviour or externalizing symptoms. These authors also noted that the methodologic aspects of individual studies were poorly reported. Macdonald and colleagues (2006) commented that those studies in which the presence of PTSD symptoms was an inclusion criterion showed a positive effect on this outcome.

Both systematic reviews recommended that CBT be considered as the first-line treatment for sexually abused children and their families, but the evidence for benefits is not as broad or robust as others have concluded. Ramchandani and Jones (Ramchandani & Jones, 2003) emphasized the importance of the following considerations for an appropriate program: 1) ensuring the child's safety from further abuse; 2) taking into account the context, including other adversities for the child and family; 3) recognizing co-existing psychiatric conditions and 4) understanding the need for outreach, given the high attrition in many of the treatment studies. These issues are applicable to protecting children from the consequences of being exposed to any type of maltreatment.

As Stallard (2006) noted, randomized controlled trial attrition rates were often not adequately reported, and intention-to-treat analyses were not used.[4] Very few studies had follow-up periods extending beyond 12 months. Between 16 to 40% of children with PTSD who received CBT still met the diagnostic criteria for PTSD at the end of treatment (Stallard, 2006). In the most recent review of psychological treatments for children and adolescents exposed to traumatic events (Silverman et al., 2008), trauma-focused-CBT (CF-CBT) (see Textbox 5.6) (Cohen, Deblinger, Mannarino, & Steer, 2004; Deblinger, Lippmann, & Steer, 1996; Deblinger, Steer, & Lippmann, 1999) was the only intervention designated as a "well-established" treatment, according to the criteria of Chambless and Hollon (Chambless et al., 1998). Although TF-CBT has the best evidence to date for treatment of PTSD symptoms following exposure to sexual abuse, the studies have been limited in power, duration of follow-up, and by lack of intention-to-treat analyses.

c. Emotional abuse

There is no single approach that has been used to reduce the recurrence of, or impairment associated with, exposure to emotional abuse. There is a paucity of high-quality studies evaluating the effectiveness of interventions specifically designed for parents or caregivers who emotionally abuse their children. The available evidence includes a comparison of two group-based versions of CBT (standard and enhanced versions of the Triple P parenting program) directed at psychologically abusive parents (Sanders et al., 2004). The standard program aimed to teach parents child management strategies designed to promote children's competence and development, and to help parents manage misbehaviour; the enhanced program included additional components aimed at changing parental misattributions and anger by challenging

[4] An intention to treat analysis counts each individual as included in intervention group or control group, based upon how they were originally assigned, regardless of whether or not they received the intervention or, in the case of controls, if they received it anyway. This form of analysis, although conservative, best reflects the real world impact of programs.

beliefs about behaviour and negative practices, as well as the introduction of planning strategies to manage anger. Both treatment groups made substantial gains in a range of outcomes; however, the treated samples may not have been representative of emotionally abusing parents.

One study compared a preschooler parent psychotherapy program (PPP) with a psycho-educational home visiting program (PHV) and a community standard intervention group (CS). The results seemed to favor a psychotherapeutic intervention in terms of improving children's negative representations of their mother and of themselves, as well as children's expectations of the mother-child relationship. However, the measurement of this particular construct was potentially biased toward identifying the benefits of the psychotherapeutic intervention (PPP) (Toth, Maughan, Manly, Spagnola, & Cicchetti, 2002).

d. Exposure to Intimate Partner Violence (IPV)

Recent trials of interventions for children exposed to IPV show positive outcomes. Lieberman et al. (Lieberman, Van Horn, & Ippen, 2005) conducted a randomized controlled trial to evaluate the effectiveness of Child-Parent Psychotherapy (CPP; see Textbox 5.7) in mother-preschooler dyads where the mother was a victim of IPV and had confirmed that the child (aged three to five years) had been exposed. The CPP group showed a significant improvement across time compared with controls, including having fewer CPP children meeting the diagnostic criteria for traumatic stress disorder. These effects persisted at six months' follow-up (Lieberman, Ghosh Ippen, & Van Horn, 2006). While this was a rigorous randomized controlled trial, the sample was relatively small. However, these results, alongside efficacy trials[5] of child-only compared to child-mother therapy and to controls (Graham-Bermann, Lynch, Banyard, DeVoe, & Halabu, 2007) indicate that these forms of mother-child therapy in families where children are exposed to IPV warrant further evaluation.

Jouriles and colleagues (Jouriles et al., 2001) evaluated an intervention (Project Support) that included provision of support and teaching about child management skills to mothers recruited from domestic violence shelters with at least one child exhibiting conduct disorder symptoms (see Textbox 5.8). Results of this small RCT showed that children in families in the experimental condition showed greater reduction in conduct problems compared with the control group at the 16-month follow-up (eight months following services). There was also a reduction in the proportion of children with externalizing problems at levels that were clinically important two years after cessation of treatment (15% of children in the intervention group versus 53% of children in the control group; (Macdonald et al., 2006)). There were also improvements in the proportion of children exhibiting clinically important levels of internalizing symptoms: 0% in the intervention group versus 35% in the control group. Of note, however, there were no differences between groups in mean levels of externalizing or internalizing problems. A second larger trial of Project Support also found greater reductions in conduct problems for children in the intervention condition compared with the control group with effect sizes in the medium to large range (Jouriles et al., 2009).

[5] In contrast to an intention to treat analysis, an efficacy trial is designed to answer the question, 'can the intervention work under ideal conditions?' In this case study subjects are analyzed according to whether or not they actually received the intervention and controls that, nonetheless, received intervention are usually excluded.

In a RCT of a family-centred strengths-based advocacy intervention for abused women and their children, there was preliminary evidence for increases in some but not all subscales of self-competence among children in the intervention group compared with the control group (Sullivan, Bybee, & Allen, 2002). The intervention included advocacy for both mothers and their children and a ten-week support and education group for the children. There was no difference between groups in maternal report of assailant's abuse of the child. The authors emphasized the preliminary nature of these findings, given the relatively small sample size and the short time frame (four-month intervention and four-month follow-up).

A recent trial of Trauma-Focused Cognitive Behavioural Therapy TF-CBT examined its effectiveness in comparison to child-centered therapy (CCT) for children with posttraumatic stress disorder symptoms related to IPV exposure (Cohen, Mannarinoa, & Murray, 2011). Children between the ages of seven and 14 years, with at least five IPV-related PSTD symptoms and a mother who had experienced IPV, showed significantly greater improvement in PTSD and anxiety following TF-CBT compared with CCT. However, this study had a high dropout (almost 40%) and children had high rates of repeated trauma exposure, highlighting the need to focus on preventing IPV recurrence in caregivers in addition to reducing impairment in children.

e. Out-of-Home care

Maltreated children are placed in out-of-home care at increasing rates across Canada. There were an estimated 67,000 children in out-of-home care on any one day across Canada in 2007, a rate of 9.2 children in care for every 1,000 children. This represents a 60% increase in the incidence of placement over the past 15 years (Mulcahy & Trocmé, 2010). In a recent cross-national study, Canada was reported to have the highest rate of children in out-of-home care of any country (Thoburn, 2007, p. 14). While the majority of these children return home within a year of being placed, others end up in longer-term arrangements ranging from placement with relatives (kinship care or guardianship) to long-term foster or group care to adoption (Courtney, 1995; Trocmé et al., 2009).

i. Preventing maltreatment recurrence

Out-of-home care is designed first and foremost to prevent maltreatment in situations where a child is considered to be at significant risk of maltreatment at home. Evaluating the efficacy of out-of home care as a protective intervention poses significant challenges. Jonson-Reid and Barth (Jonson-Reid & Barth, 2003) found that 14% of 1915 reunified children experienced a substantiated maltreatment episode within four and half years of exiting foster care. Rates were highest for children with shorter stays in out of home care. A seven and half year follow-up study of placed and non-placed children found that 70% of children who had been in care were re-reported because of suspected maltreatment (Drake, Jonson-Reid, & Sapokaite, 2006). Rates of re-entry to care have been found to range from 20% to 40 % (Courtney, 1995; Terling, 1999; Wulczyn, 2004). Estimates of recurrent maltreatment among children remaining in parental custody range from 17% to 35% within a five-year period (DePanfilis & Zuravin, 1999; Fluke, Shusterman, Hollinshead, & Yuan, 2005).

ii. Preventing impairment

A secondary objective of out-of-home care is to minimize the effects of maltreatment experienced prior to placement. Studies examining the effects of out-of-home care on maltreated children's emotional, social and cognitive development have generally found limited evidence of the efficacy of placement. The previously described study comparing children in out-of-home care to children kept at home through experimental legislation introduced in two counties in California found at follow-up that foster children were doing marginally better in terms of academic outcomes, while there were no differences between the two groups in social and emotional functioning (Wald, Carlsmith, Leiderman, Smith, & French, 1988). Compared to matched non-maltreated peers, however, both groups of maltreated children had deteriorated significantly. Two studies using administrative data to follow large retrospectively matched cohorts found few differences in outcomes between maltreated children placed in foster care compared to maltreated children who remained at home (Runyan & Gould, 1985; Widom, 1991). A third study found lower delinquency rates for children who remained at home (Jonson-Reid & Barth, 2000).

Comparing maltreated children placed in foster care at a young age to non-placed maltreated children, a prospective longitudinal study found higher rates of behavioural problems in the placement group (Lawrence, Carlson, & Egeland, 2006). In contrast, a study of cortisol production patterns in young children involved with child protective services living at home compared to children in foster care found that children who remained at home had greater perturbation to the diurnal pattern of cortisol production, indicating that foster care may have a regulating influence on children's cortisol among children who have experienced maltreatment (Bernard, Butzin-Dozier, Rittenhouse, & Dozier, 2010).

Few studies have examined the impact of length of time in foster care, although child welfare policies in most jurisdictions in Canada and the United States have stressed early reunification, and statutes in many jurisdiction set limits on length of out-of-home placements. A six-year follow-up study comparing youth who return home to those who remain in longer term foster care raises questions about the benefits of early reunification without adequate home support services (Taussig, Clyman & Landsverk, 2001). After controlling for age, gender and behavior problems measured within their first 6 months in care, the study found that reunified youth were more likely to engage in risky behaviors, to have dropped out of school, to have received lower grades and to report more behavior problems (Taussig et al., 2001).

Interpretation of this body of studies is challenging given variations in the populations studied and the measures used, as well as the challenges inherent in adequately matching children at home with children in out-of-home care on exposure to, and severity of, maltreatment. A promising design that attempts to provide better matching was piloted recently in a study using statistical modelling of child protection investigators' placement tendencies to create two matched groups of placed and non-placed children (Doyle, 2007). Older children on the "margin of placement" had better outcomes in terms of juvenile delinquency, teen motherhood, and employment, when they remained at home.

iii. Comparing out-of-home care programs

Out-of-home placements range from family based care (including foster-care, treatment foster-care and kinship care) to staff-based care (including group homes, residential treatment centres, and other institutional settings). Research comparing different forms of out-of-home care point to some promising programs. In particular, there may be potential benefits from enhancing foster care with therapeutic components designed to address emotional and behavioural problems displayed by some children in out-of-home care. A systematic review of five quasi-experimental studies suggests that treatment foster care may be a useful intervention for children and young people with complex emotional, psychological and behavioural needs, although these interventions did not specifically target maltreated children (Leve, Fisher, & Chamberlain, 2009; Macdonald & Turner, 2008). A particularly promising model is the Casey Family Program foster homes that provide enhanced treatment components in addition to extensive training of foster parents. A one to 13 year follow-up study of 479 foster care alumni who were placed in Casey foster homes as adolescents found that, compared to a matched group of youth placed in regular public foster homes, the youth in the model programs spent two years longer in care and had significantly fewer mental disorders (major depression, anxiety disorders, and substance use disorders) than did public program alumni (Kessler et al., 2008). For younger children, three randomized controlled trials of attachment-based treatment foster care programs found improvements in attachment, cortisol, and behavioural measures for young children in the specialized foster care programs compared to children in regular foster care (Fisher, Gunnar, Dozier, Bruce, & Pears, 2006).

Beyond the promising results from adding therapeutic components to out-of-home care, there is growing evidence that, even without a treatment component, some forms of care may be more beneficial than others. A systematic review of 62 quasi-experimental studies comparing kinship care to non-relative foster care concluded that children in kinship foster care experienced better behavioural development, mental health functioning, and placement stability than do children in non-kinship foster care (Winokur, Holtan, & Valentine, 2009). While encouraging, these results must be interpreted with some caution given the difficulty inherent in controlling for pre-placement differences between children in kinship and non-relative foster homes (Koh & Testa, 2011).

Comparing foster care to institutional care, a recent randomized controlled trial in Romania found that children in foster care had better cognitive outcomes compared to those who remained in an institutional setting (Nelson et al., 2007).

4. Summary and conclusions

Responses to child maltreatment have focused first and foremost on reporting and investigating: over three million children in the United States are reported each year to child protection services (U.S. Department of Health and Human Services & Administration for Children and Families, 2010) and over 200,000 children per year are reported in Canada (Trocmé et al., 2010). A much smaller proportion of children receive services as a result of these investigations. Unfortunately, few of these services are based on intervention models that have been evaluated, or have even been described (see Textbox 5.9 for how this applies to Canada). Despite consistent evidence of

the severe and long-lasting effects of child maltreatment, research on how best to intervene to prevent maltreatment and its recurrence is surprisingly limited. The evidence reviewed in this chapter suggests that effective responses require a much higher intensity of services than are currently being deployed. Furthermore, given the overlap among the five major subtypes of child maltreatment as outlined earlier, it is surprising that more interventions do not consider integrating approaches to prevention, especially for those types that show common risk factors, such as child physical abuse and IPV.

The strongest evidence of program effectiveness has emerged from intensive targeted programs designed *to prevent child abuse and neglect*. The program with the best evidence for preventing child physical abuse and neglect is the Nurse-Family Partnership, in which reductions in child maltreatment and associated impairments have been reported that have been sustained for up to 15 years. Attempts to adapt the program using less structured or less intense services have not been found to be effective. The Triple P-Positive Parenting Program, a population-based prevention model that involves increasingly intense levels of intervention tailored to the needs of different groups of parents, has shown promising results with maltreating families in a community level randomized controlled trial, but further replication is required with individual-level data before firm conclusions can be drawn.

Because of the very early and relatively specific age of infants at risk for shaken baby syndrome/abusive head trauma, the clear relationship to crying as the main stimulus, and the specific caregiver behaviour (shaking), education programs targeted to parents in the perinatal period are feasible and have shown promise (Barr et al., 2009a; Barr et al., 2009b; Dias et al., 2005). However, their effectiveness in reducing the incidence of SBS/AHT requires replication. It is becoming increasingly clear that, not only shaken baby syndrome, but all forms of infant abuse have a similar age-specific incidence (Leventhal, Martin, & Asnes, 2010) and probable relation to normal crying as a stimulus. This implies that similar prevention strategies might be effective in preventing infant abuse generally. Specific training of physicians delivering pediatric care may also be useful, but effectiveness trials in real-life practice settings are not yet available. Promising results from the evaluation of attachment-based interventions show a reduction in maternal insensitivity, a precursor of some forms of emotional maltreatment.

There is far less evidence for the effectiveness of prevention efforts targeting other forms of maltreatment. Prevention programs targeting sexual abuse face a particular challenge given that they have tended to focus on the potential victims rather than the perpetrators, and have focused on knowledge and awareness rather than victimization. We found surprisingly limited evidence for effective prevention programs to reduce either IPV or the effects of exposure to IPV on children.

Evidence for the effectiveness of interventions to prevent the *recurrence* of maltreatment has been challenging. Recent findings from a statewide trial of SafeCare to reduce recidivism are promising, however. PCIT has also shown benefits in the reduction of recurrence of physical abuse, but not neglect. Perhaps not surprisingly, maltreating parents have not responded as effectively to parent training programs as have other types of parents. Results for the evaluation of an intensive home visiting program, based on the principles of the NFP program that was provided to families where abuse or neglect had already occurred, were disappointing. These

results further underscore the difficulties inherent in bringing about change in situations where maltreating patterns of parenting are already well established. Given the emphasis that has been put on detecting and investigating child maltreatment, it is surprising that programs to prevent the recurrence of child maltreatment have not been better developed and evaluated.

More progress has been made in developing approaches to *reduce impairment*. For children with symptoms of posttraumatic stress disorder (PTSD) following exposure to child sexual abuse, there is evidence for the effectiveness of cognitive behavioural therapy (CBT) in reducing such symptoms. However, this treatment ideally involves a non-offending parent who is committed to assisting the child with the CBT program. Since others types of child maltreatment such as neglect often co-occur with sexual abuse, implementing this program for a child without adequate parental support should not be assumed to achieve the same outcomes. It is encouraging that Trauma Focused-CBT has been shown to be effective in increasing PTSD remission among children exposed to IPV. The trial by Cohen and colleagues (Cohen et al., 2011) is an important example of how a treatment for symptoms associated with one type of maltreatment (sexual abuse) can also be effective for symptoms related to another exposure (IPV). However, it should be noted that the treatment is targeted to assist children with PTSD symptoms; that is, it is not applied based simply on the exposure without consideration of the child's specific presenting problems. Child-parent psychotherapy has also shown benefits for children exposed to IPV, as has an intervention for mother-child dyads that included support and child management skills for mothers.

While out-of-home placement presumably provides short-term protection from the recurrence of maltreatment at home, there is still little evidence that these placements lead to significant and lasting improvements for children. One of the difficulties with many such placements is that there are few interventions targeting parents while their children are in out-of-home care. Without significant improvements in their parents, it is not surprising that some children are re-victimized when they are reunified with their families and end up returning to out-of-home care. Nevertheless, in contrast to policies that emphasize early reunification, foster care placement can lead to benefits for abused or neglected children compared with those who remain at home or who reunify from foster care. Out-of-home placements in programs that include well-defined therapeutic components for the children have yielded more positive results. Out-of-home care appears to be more effective when it goes beyond short-term protection and is designed to address impairment resulting from past maltreatment.

Overall, the results of research on the effectiveness of prevention of child maltreatment and of impairment are consistent with the research from the previous chapters. The key messages are:

1. **The success of intense and sustained prevention programs targeting high-risk families during the perinatal period and early childhood is consistent with the research reviewed in previous chapters pointing to early childhood being a high priority window for intervention.**

2. **The limited evidence of the efficacy of interventions targeting families where maltreatment has already occurred is consistent with research evidence that patterns of parent-child interactions are difficult to change at later stages of**

development and that children's development has already been influenced in response to these negative interactions.

3. **While poverty is a key risk factor for child maltreatment, poverty is rarely addressed by child maltreatment prevention and intervention programs.** This is part of a larger discussion dealing with broader population health approaches that is largely outside the scope of this chapter. Textboxes 5.9 and 5.10 touch on some of these approaches, but the reader is referred to the concluding section for further discussion.

4. **Child protection programs have been developed around a case identification system that focuses on reporting and investigating individual incidents of maltreatment, while placing less emphasis on assessing child functioning and quality of parenting.** The evidence from the literature indicates, however, that in most situations it is the chronic exposure to maltreatment, poor parenting and other adversity rather than an individual occurrence of maltreatment that is most damaging, and that the effects of this chronic exposure are particularly severe for some children. A "harm reduction model" that focuses less on predicting risk of maltreatment and preventing recurrence of individual events than emphasizing development of protective factors may be more successful in minimizing the occurrence and effects of adverse events.

As stated at the outset, this chapter provides an evidence-based overview of what we know from the peer-reviewed literature about the effectiveness of specific interventions in reducing child maltreatment and associated impairment. We acknowledge that other approaches may reduce addiction and mental health problems in teenage and young adulthood without the primary focus of intervention being child maltreatment. This is a huge field, beyond the scope of this Report. Nonetheless, Textbox 5.10 has been included to indicate the kind of promising approaches we think deserve ongoing consideration.

Textbox 5.1. Nurse Family Partnership (NFP)[6]

Program Model

- home visitation based on theories of human ecology, self-efficacy and human attachment
- program promotes responsive and sensitive care-giving by assisting mothers to review their own childrearing histories and making decisions about how they want to parent their children
- nurse visitors develop a trusting relationship with the mother and other family members to promote sensitive, empathic care of their children

Program Goals

- improving pregnancy outcomes by assisting women to improve their prenatal health-related behaviours
- improving children's postnatal health and development by helping parents care for their child
- improving parents' economic self-sufficiency by assisting them to plan for their future

Program Description

- home visiting by nurses with Bachelor's of nursing degree (RN in the Elmira trial); they underwent four weeks of training prior to the program
- women who were pregnant for the first time and of low socioeconomic status were recruited from antenatal clinics before 29 weeks gestation (before 25 weeks in the Elmira trial)
- frequency of home visits changed with stages of pregnancy and adapted to parents' needs; in the three trials, nurses completed an average of 6.5 to 9 visits prenatally and 21 to 26 visits from birth to the child's second birthday; visits lasted approximately 75 to 90 minutes
- nurses follow detailed curriculum guidelines

[6] Adapted from (MacMillan et al., 2009)

Textbox 5.2. Early Start Program[7]

Program Model

- intensive home visiting service for families based on a social learning-model approach
- critical elements include: 1) assessment of family needs and resources; 2) development of a positive partnership between client and family support worker; 3) collaborative problem-solving; 4) provision of support, advice and mentoring to mobilize families' strengths and resources

Program Goals

- improving child health
- reducing risk of child abuse
- improving parenting skills
- encouraging family socioeconomic and material wellbeing
- encouraging stable partnerships

Program Description

- home visiting by nurses or social workers, Bachelor's level-prepared; they were given a five-week training program
- nurses referred any families with two or more risk factors on an 11-point screening measure that included parent and family functioning, plus those where nurses had concerns re client's ability to care for the child
- one-month period to assess family needs; those that scored above a cut-point indicating problems in family functioning were offered full program
- services were tailored to meet the needs of the family
- families were seen on average over 50 times in the first year; services were available for up to five years

[7] Adapted from (MacMillan et al., 2009)

Textbox 5.3. Triple P - Positive Parenting Program (PPP)[8]

Program Model

- public health population-based approach to child maltreatment
- comprehensive population-level system of parenting and family support
- multiple levels of social learning based program to meet the needs of different groups of parents

Program Goals

- address the difficulties of limited population reach via evidence-based parenting programs
- enhance parental competence and reduce dysfunctional parenting practices

Program Description

- multilevel system including five intervention levels of increasing intensity and restricting population reach and delivered by a range of specially trained practitioners
- universal Triple- P: use of media and informational strategies such as website information and community events, among others
- selected Triple-P: Comprises brief and flexible consultations with individual parents each; and/or parenting seminars with large groups of parents
- primary care Triple-P (level 3) four brief consultations incorporating active skills training and use of parenting tip sheets
- standard and group Triple P (level 4) comprising 10 session program with individual families utilizing active skills training, home visits or clinic observation sessions or 8-session group administered program using observation, discussion, practice and feedback + telephone follow-up sessions
- enhanced Triple P (level 5) comprising enhanced version of level four e.g., optional modules on partner communication, mood management and stress coping skills

[8] Adapted from (MacMillan et al., 2009)

Textbox 5.4. Parent-Child Interaction Therapy (PCIT)[9]

Program Model
- PCIT involving the treatment of parents alongside children
- Behaviourally defined approach to skills training

Program Goals
- To increase parental motivation and enhance skills
- To improve parent-child interaction through use of direct coaching and practice of skills in dyadic parent-child sessions

Program Description
- Three modules delivered by PCIT trainers who ranged in experience from graduate students to experts with years of training in PCIT
- Parent-child dyads referred as they entered the child protection system for a new confirmed physical abuse report
- Module 1: six-session orientation group aimed at increasing motivation by fostering an understanding of the negative consequences of severe physical discipline and development of self-motivational cognitions and self-efficacy expectations
- Module 2: 12 to 14-session course of PCIT comprising clinic-based, individual parent-child dyad sessions in two phases. Phase 1 (Child Directed Interaction) focuses on teaching relationship enhancements skills and establishing a daily positive interaction; Phase two focuses on teaching command giving skills and a behavioural discipline protocol to promote the child's compliance
- Module 3: four-session follow-up group program to address any implementation problems; children attend a concurrent social skills program

[9] Adapted from (MacMillan et al., 2009)

Textbox 5.5. SafeCare

Program Model
- Manualized structured behavioural skills training
- Addresses parent/child or parent/infant interaction (caregiving structure, parenting routines); home safety and child health

Program Goals
- To reduce child protective services recidivism

Program Description
- Can be delivered as freestanding program or as one component of a broader home visiting service. The latter was the case for the trial by Chaffin et al. (Chaffin et al., 2012) where caregivers were enrolled in a statewide system of home-based services operated by community-based agencies
- Usually program is provided to families where there is one preschool age child in home and no untreated substance use disorder. For the trial by Chaffin and colleagues (2012), families with children up to 12 years of age irrespective of substance use were included.
- Based on the website (http://chhs.gsu.edu/safecare/), modules include Health, Home Safety, Parent-Child/Parent-Infant Interactions, Problem Solving and Counseling
- Training occurred in small 1-week workshops involving live skill demonstration and role play followed by one observed field session and then regular supervision

Textbox 5.6. Trauma-focused Cognitive Behavioural Therapy (TF-CBT)[10]

Program Model
- Psychotherapeutic intervention based on cognitive and learning theories

Program Goals
- to alleviate symptoms of posttraumatic stress disorder (PTSD) and related difficulties experienced by children exposed to either sexual abuse or IPV

Program Description
- sessions provided by trained mental health professionals with diverse backgrounds (e.g., social workers, psychologists) who underwent three days of training
- children and their families recruited from outpatient clinical programs where referrals made from broad range of providers (e.g., police, child protection workers) plus self-referrals
- specific elements include skills in expressing feelings, coping, recognizing links between feelings and behaviours; gradual exposure through developing a child's narrative; reprocessing the abuse; psychoeducation about child sexual abuse or IPV, depending on the nature of the exposure, and safety; parent management skills
- in one trial, treatment was provided in 12-weekly individual sessions to parents and children with 45 minutes for each individual session; three sessions included a joint parent-child session for 30 minutes (total of weekly sessions 90 minutes)

[10] Adapted from (MacMillan et al., 2009)

Textbox 5.7. Child-Parent Psychotherapy (CPP)[11]

Program Model

- focus on the mother-child relationship
- based on theories of attachment, parenting and traumatic stress, including social learning and cognitive-behavioural theories and the intergenerational transmission of violence

Program Goals

- to reduce children's emotional and behavioural problems and posttraumatic stress symptoms
- to reduce maladaptive behaviours and support developmentally appropriate interactions
- to assist the mother and child in creating a narrative of the traumatic events while moving towards resolution

Program Description

- clinicians had Master's and PhD-level training in clinical psychology and were trained using a CPP manual developed for this purpose.
- CPP provided to mother-preschooler (aged 3 to 5 years) dyads where the mother was a victim of IPV and the child had been exposed to IPV
- the mother was actively involved in setting the treatment plan and received individual counseling as required
- weekly 60-minute CPP sessions for 50 weeks including child's free play with appropriate toys to elicit trauma play and social interaction

[11] Adapted from (MacMillan et al., 2009)

Textbox 5.8. Project SUPPORT

Program Model

- includes two primary components: 1) teaching mothers child management skills and 2) providing mothers with support during their transition from the shelter

Program Goals

- to reduce children's conduct problems
- to improve mother's parenting

Program Description

- eligible participants include women who entered shelters with 4- to 9-year-old children and who had reported experiencing at least one act of physical IPV from a male partner during the previous year; the child had to meet the criteria for oppositional defiant disorder or conduct disorder
- child management skills component was modeled after other behavioural parent training programs and includes 12 skills (e.g., listening to your child)
- support component was both instrumental and emotional and was based on advocacy intervention for women leaving shelters (Sullivan & Bybee, 1999)
- child problems; children attend a concurrent social skills program
- intervention was delivered by trained therapist (Master's level and one clinical psychologist) accompanied by undergraduate or post baccalaureate students; after completing mastery test and accompanying senior therapist in delivering intervention, trainee therapists could then deliver intervention
- therapists worked mainly with the mothers, although children could be brought into the sessions; students served as child mentors for target children
- mothers taught skills through didactic instruction with written materials, role plays, feedback, homework and mastery checks
- families could receive support for up to eight months after leaving shelter; average number of home-based sessions was 20

Textbox 5.9. Intervention in Canada

Implementation of evidence-based interventions in Canada

It is difficult to determine the extent to which evidence-based interventions to prevent child maltreatment and its impairment are implemented in Canada, other than for those interventions where dissemination of the program is monitored and/or under the control of the person or group who developed the intervention. For example, the NFP, which is only implemented with agreement from Dr. David Olds, is available on a pilot basis in Hamilton, Ontario and is about to undergo a province-wide evaluation in a randomized controlled trial in British Columbia. Triple P, considered a promising intervention, is available in some provinces, but the extent of its dissemination and adherence to the original fidelity is unclear. For example, Manitoba is currently piloting a Teen Triple P Program that includes an equity-focused component for specific groups of teenagers. This is also the case for PCIT and TF-CBT. British Columbia is the site of a province-wide trial of the Period of *PURPLE Crying* shaken baby syndrome/abusive head trauma prevention currently being evaluated, but it has also been implemented in other provinces and communities across Canada.

Notwithstanding this, below are three promising, Canadian-based intervention programs:

• A program adapted for Ontario by the Centre for Addiction and Mental Health, *Ontario's Strengthening Families for the Future,* targets families with younger children aged seven to 11, who may be at risk as adolescents for academic failure, poor mental health, substance abuse and/or delinquency(Butler-Jones, 2011). The program works to improve communication and relationships within a family, building skills that will allow families to solve the more complex problems of adolescents and improve the life skills and resilience of the adolescent. Long-term evaluations of the Strengthening Families Program (SFP) in the United States has shown positive outcomes for youth, delaying the age at which alcohol is first consumed and decreasing illegal drug use (Foxcroft, Ireland, Lister-Sharp, Lowe, & Breen, 2003; Spoth, Redmond, & Shin, 2001).

• The Longitudinal Montreal Prevention Experiment targeted 7-9 year old boys who had been identified by Kindergarten teachers with very disruptive behaviour. Parents were taught family management skills, interaction techniques that use praise and reward and mild negative consequences and child monitoring skills based on procedures developed by the Oregon Social Learning Center. Boys were taught prosocial skills in small groups during the first year of the program and self-control techniques in the second year. An RCT evaluation at the age of 12 found the boys in the treatment group had less antisocial behaviour and a higher percentage in age appropriate classes than untreated controls (McCord, Tremblay, Vitaro, & Desmarais-Gervais, 1994). Long-term follow up showed at age 24, found a significantly higher percentage of boys in the treated group graduated from high school and a lower percentage were involved with criminal behaviour than their untreated controls. High school graduation rates and criminal records were not significantly different from a normative (low-risk) group of boys followed in the experiment (Boisjoli et al., 2007).

Better Beginnings, Better Futures (BBBF) is a 25-year longitudinal prevention research project aimed at providing information on the effectiveness of prevention as a policy for children. Begun

by the Ontario government in 1991, BBBF was based on a comprehensive, community-based model of primary prevention for families with young children in three high-risk communities. The model was designed to prevent long-term social, emotional and educational problems in adolescents and adults, which have their genesis in early childhood, by improving family and community life for children in the four to eight-year-old age range and their parents. Using a quasi-experimental longitudinal research design, data were collected from a longitudinal research group of 959 children from Kindergarten to Grade 3 and their families in the three project sites and in two demographically matched comparison neighborhoods. Follow-up data were again collected when these children were in Grades 6, 9, and 12. In Grade 12, 10 years after ending their program involvement, BBBF youth had higher average marks, used special education services less, and were less likely to be involved in committing property offences. Fewer BBBF parents were clinically depressed, and they reported drinking alcohol less frequently and having fewer smokers in the home. Both BBBF youth and parents rated their neighbourhoods more positively. Results of an economic analysis of BBBF indicated that the government saved approximately $4,500 per family, or $2.50 for each $1.00 invested in the project.

Broad-based approaches being taken in Canada

The Public Health Agency of Canada asserts that the most effective mental health interventions, particularly for at risk youth must be sustainable over time, gender sensitive, developmentally and culturally appropriate, tackle several problem areas at the same time and target not only youth but families and communities. Several examples of this approach follow.

• Canada has a focus on schools as healthy settings for teens with an increased reliance on training teachers to identify mental health issues and to be capable of providing in-class programs that enhance the work of health and social-care professionals (Butler-Jones, 2011).

• The Evergreen framework, developed under the auspices of the Mental Health Commission of Canada (Kutcher & McLuckie, 2010), aims to serve as a resource for child and youth mental health professionals, stakeholders and policy makers by presenting a set of values upon which services and initiatives should be based. The document identifies strategic directions and specific recommendations for mental health promotion, preventions, interventions and on-going care as well as for research and evaluation.

• Programs developed to address homelessness in Canada have not been subject to rigorous evaluations. Nevertheless, an important shift to collective and proactive approaches away from reactive, individual approaches has begun within some organizations serving homeless youth in Canada, where socio-political issues are explored and inequality challenged.

• The International Resilience Project (IRP), a Canada-led multinational project, was designed to study aspects of resilience across cultural contexts that account for positive outcomes among youth (Ungar, 2006; Ungar & Liebenberg, 2005). Fourteen sites across 11 countries (including an Aboriginal community in Northern Canada; as well as sites in Halifax and Winnipeg) were chosen to maximize variability both in the risk factors facing children and the characteristics of the children themselves. Across the settings a convenience sample of 1451 adolescents (694 males = 47.9%; 757 females = 52.1%; mean age = 16 years) participated in a quantitative survey

and another 89 individuals were interviewed in-depth. The survey identified a consistent set of resiliency characteristics for boys and girls from southern Canadian and American sites. A second group with a distinct set of common characteristics was girls (though not boys) in non-western sites and aboriginal girls in Northern Canada. The qualitative studies identified seven tensions that appeared to account for patterns in how resilience manifested itself: access to material resources; relationships; identity; power and control; cultural adherence; social justice and social cohesion. Youth that experience themselves as resilient, and were also identified by their communities as resilient, seemed to be those who successfully navigated their way through these tensions with the strengths and resources available within themselves, their families, communities and culture.

Textbox 5.10. Promising interventions that do not specifically address child maltreatment

• The Incredible Years Program, a combined parent–school Intervention includes parent, teacher, and social skills training components. In the parent component, parents are shown brief videotaped vignettes of parent–child interactions as examples of positive interactions and communication with their children, the value of praise and reward, as well as the use of mild negative consequences such as time-out among others. The teacher component focuses on effective preschool and elementary classroom management and the social skills component teaches children social skills using puppets. Extensive evaluations for children identified with conduct disorders and for preventing aggression and related problems in children whose behaviour is not yet at the clinical level have shown improvements in positive parenting practices and reduction in harsh parenting as well as reductions in problem behaviours (Gardner, Burton, & Klimes, 2006; Linares, Montalto, Li, & Oza, 2006; Patterson, Reid, & Eddy, 2002; Reid, Webster-Stratton, & Beauchaine, 2001). Benefits have been shown for a variety of ethnic groups (Patterson et al., 2002; Reid et al., 2001) and when provided by diverse professionals, including teachers, nurses, family support specialists, and social workers (Gardner et al., 2006; Hutchings et al., 2007).

• Three US comprehensive early education programs that sought to improve educational outcomes for young children by a focus on cognitive and language skills and small class sizes are reviewed by Reynolds and Temple (Temple & Reynolds, 2007); the Perry Preschool Program and the Carolina Abecedarian project, both evaluated in randomized controlled trials, and the Child-Parent Centers (CPC) employing a comparison condition. The Perry Preschool Program and CPC included a parent intervention, while the Carolina Abecedarian project did not. Follow-up assessments into adulthood including at least 87% of study participants were conducted on all three programs. Child outcomes included improvements in academics, including lower use of special education services, lower grade retention, higher grade completion, higher rate of high school graduation, higher rates of college attendance, fewer arrests by age 19 (two programs), higher rates of employment (in the two programs that assessed this outcome), and higher monthly earnings (assessed by one program). Additional program benefits found included less child maltreatment (in the only program that assessed this outcome). Reynolds and Temple (Temple & Reynolds, 2007) conclude that the benefits of these programs exceeded their costs. A meta-analysis by Aos, and colleagues (Aos et al., 2004) of these and other early child childhood education programs draws a similar conclusion. See Chapter 2 for more details.

CHAPTER SIX: CONCLUSIONS

The general purpose of this report was to review the evidence regarding the putative impact of ACE on mental health problems and unhealthy behaviours in adolescence and young adulthood. The report also aimed to document the bio-psycho-social processes through which these early adversities may have their impact on development; to examine the evidence for the role of protective factors; and to evaluate the effectiveness of a variety of interventions designed to mitigate the adverse effects of these early environmental influences.

1. Synopsis of findings

The last ten years have seen the coming of age of both older and new cohort studies, including some conducted in Canada, that clearly converge in showing a predictive association between various early childhood adversities and a variety of maladaptive outcomes later in life (see Chapter 2). This association is robust in that it has been confirmed (1) for a variety of ACE, ranging from chronic stressors such as family poverty and inappropriate care, to discrete episodes of child maltreatment; (2) for a wide range of outcomes, such as emotional and behavioural problems including depression and anxiety disorders, school difficulties, delinquency, criminal offending, and adaptations to stress; (3) in studies with various designs, such as retrospective and prospective longitudinal studies, and populations, such as community-based and high-risk children samples; (4) in studies designed to investigate individual differences by taking into account the interplay between genes and the environment.

At the same time, new findings in neuroscience, genetics, and epigenetics have started to elucidate the biological pathways and the conditions under which ACE may have a long-term impact. There is converging evidence that early life stress is associated with long-term changes in brain circuitry, dysregulation of the autonomic nervous system and endocrine regulation and a host of other neurobiological changes that, in turn, influence health and quality of life across the lifespan. Clearly, the inequalities in physical, social/emotional, and cognitive development that emerge early in life are largely accounted for by the interplay of genetic factors and early environments (see Chapters 2 and 3). Early childhood is a sensitive period during which the environment may modify the brain circuitry, especially that governing the emotion, attention, self-control and stress systems of the child; and it is increasingly clear that the environment may change the way genes are expressed through epigenetic processes (see Chapter 3). There is also emerging evidence that the biological systems and pathways linking ACE to biology and behaviour also extend to the regulation of parenting behaviours (see Chapter 4), thus shedding new light on the intergenerational transmission of parenting. Finally, there is now a limited but promising body of research on programs designed to reduce child maltreatment, perhaps the most serious ACE, and its associated outcomes (see Chapter 5). The emerging evidence is that child maltreatment and its associated outcomes can be reduced if specifically targeted, intensive and sustained services are deployed. This is encouraging, but much remains to be done in this area. Many programs show promise but replications are clearly needed. Moreover, there is a paucity of credible research evidence on how broader interventions at the level of the community might influence ACE in ways that, in turn, would influence long-term developmental outcomes.

2. Seven key features of an emerging perspective

The dots are not all connected, but from this new corpus of research a coherent epigenetic developmental landscape has begun to emerge in which the social environment and biology are deeply intertwined. The last decade has seen a growing integration of the biological and social aspects of developmental research to the point where the biosocial synthesis is now an imperative for any significant understanding of the developmental processes linking early adversity and negative outcomes. Here, we identify seven important features of this emerging perspective. Some of these features have clear implications for policy and practice, whereas others primarily address the direction that future research should take. Accordingly, discussion of implications for policy and practice are clearly identified following each feature(s) that it pertains to.

Feature 1

There is now clear evidence that individual differences in developmental difficulties can be established very early in life, in fact as soon as they can be reliably assessed, with a small, but significant, number of children displaying various "symptoms". These early problematic developmental pathways predict later difficulties and are typically associated with a variety of prenatal and perinatal risk factors reflecting early environmental adversity. The moderate success of early prevention programs and the limited evidence for the effectiveness of interventions at later developmental stages is congruent with the view that early childhood is a period of high plasticity in brain development, a period that progressively gives rise to the consolidation of individual differences. However, early experiences are far from being strictly deterministic. There is abundant evidence that brain development continues into early adult life, especially the executive functions of the prefrontal cortex. Adolescence is a secondary sensitive period in brain development when neural circuitry supporting critical and reflective thinking emerges; building upon the foundation of cognitive, social and emotional development that has been laid down earlier in childhood (Bardin, 2012).

Implications of feature 1 for policy and practice

This developmental pattern has two important implications for practice and policy: (1) Prevention should start early if we want to mitigate the establishment and consolidation of these adverse early developmental trajectories; (2) Any monitoring system of early childhood development should incorporate a longitudinal component to more precisely account for these changes over time.

This report is not arguing that the early years are the *alpha and omega* of developmental health, but clearly any serious prevention 'system' needs to start strong in that period, and more than at any later time in development. The data are clear about this. Nor does this report argue for an 'all or nothing' approach to assessment and prevention, but rather a balanced one where the balance is tilted towards the yearly years. We are also arguing for a *development approach with continuities* **(**clearly significant due to the persistence of risk factors, developmental inertia and cascading effects**)** *and discontinuities* **(**also clearly present**)**, whereby later developmental periods, especially adolescence, where new vulnerabilities/difficulties may arise, should also be the object of attention (and monitored accordingly). Thus, in general terms, this report supports an integrated developmental approach to services and social policy.

Feature 2
The new nebula of developmental and epidemiological research has also started to clarify the complexities of environmental influence across development. For instance, it highlights that ACE are multifaceted and multileveled, as they vary from intimate to societal. However, much of what is known about the role of ACE revolves around the proximal (e.g., parenting), rather than the distal determinants of development. Broad determinants of child development are still the parent pauvre of the new knowledge base, including interventions. This is unfortunate as environmental factors that influence whether children are going to end up with adverse outcomes are not only found at the level of the individual or family, but also at the level of the community and society, especially as they influence families embedded within them. Community and societal determinants are important, most likely, because they affect families—where most of the proximal causes are—not because they are independently causal. This knowledge gap between distal and proximal adverse environmental factors needs to be bridged in order to better understand to what extent and how the more global determinants affect child development through their impact on more proximal environments, such as the family.

Feature 3
ACE are not just about dramatic events; day-to-day interactions in children's lives are more important than we once thought they were. The research evidence increasingly suggests that the chronic, recurrent, and often routine aspects of early experiences affect development, in addition to the specific and more dramatic exposure to maltreatment. In Canada, socioeconomic gradients in child development: social-emotional, cognitive and physical, are largely driven by such day to day differences in experience (Hertzman & Boyce, 2010).

Implications of features 2 and 3 for policy and practice
Features 2 and 3 have policy and practice implications for: (1) investment in parenting, (2) addressing day-to-day living conditions through broad social change, and (3) the necessity and character of developmental monitoring systems.

Investment in the complexity of improving parenting in various contexts should be made. Parenting and family function are clearly central aspects of day-to-day adverse experiences, and thus need to be addressed seriously. Here, we emphasize that intervention programs, where there has been early adversity, need to be informed by what we understand about the mechanisms underlying the phenomenon itself and its link to later adverse outcomes. In particular what we have come to know about the normal regulation of parenting and the role of emotion, attention and reward needs to inform intervention programs.

However, we cannot and should not stop there. We can and should start building upon an extended support system by documenting (and then possibly harnessing) the nurturing qualities of childcare, early school experiences, and the community environments where growing children spend their time. Building upon support systems means addressing the day-to-day developmental conditions that could pre-empt addictions and mental health problems, through a broad model of social change; complementing more targeted interventions focused on dramatic adversities. Social change models are alluring, because they promise shifting societal norms in a positive direction, as has happened, for instance, with adult cigarette smoking in Canada. But such approaches, which are, by nature, diffuse and slow to develop, can only be conducted responsibly

if they are tied to monitoring of desired outcomes. In the case of reducing developmental health problems through social change, a monitoring system must be in place that has the capacity to evaluate four factors: whether or not the nurturing qualities of family, childcare and community are, in fact, improving; whether or not trajectories of early child development are improving; whether or not trends in developmental health in adolescence and early adulthood are improving; and, finally, whether or not the trends in developmental health problems are being influenced by changing early experiences and the state of early child development. Although this may sound ambitious, in practice different provinces in Canada have already put in place various monitoring elements that, if combined, could achieve these purposes. Importantly, a pan-Canadian effort already exists to bring these initiatives together in a coherent developmental monitoring system (Forum for Early Child Development Monitoring).

Feature 4

The intricacy of developmental processes is further augmented by the growing flow of positive feedback loops of negative events and processes across development: *child factors and factors that are external to the child tend to become developmentally intertwined through cascading effects that may spiral out of control*. Children who experience early adverse events are at an increased risk for experiencing repeated and chronic stressors at future stages of development. It is important to understand the dynamic of development in order to understand how some children may become caught in developmental traps of increasing steepness. In other words, the biological and environmental determinants are clearly intertwined in developmental pathways. The challenge for developmental science is to understand these cascading effects in order to guide prevention efforts.

Feature 5

The understanding of environmental determinants, and of their mechanisms of action is further complicated by the fact that their potential impact also depends on child factors, including genetic factors. Indeed, the role of early adversity is typically one that should be seen as conditional rather than general. In other words, not only is exposure to early adversity not randomly assigned, and fueled by positive feedback loops, but not all children so exposed are affected similarly. Clearly, *genes alone do not determine our health and behaviour*. *Neither do environments.* The new generation of longitudinal studies has successfully moved us beyond the limited "nature – nurture" dichotomy to show the ubiquity of gene-environment interactions. Nowhere is the interplay between genes and environment more evident than in the relationship between the early rearing environment of humans and vulnerability/resistance to chronic illness, cognitive, social and emotional well-being. At the same time, this G x E framework is still in the making, and does not come without challenges.

Implications of features 4 and 5 for policy and practice, and training

One of the most important challenges presented us by the G x E framework is to understand how multiple interactions combine in individuals to influence developmental trajectories. Obviously, this is a scientific challenge to meet for geneticists and developmental scientists. At the same time, this challenge evokes the more formidable issue of the successful integration of knowledge in genetics, epigenetics, basic neuroscience and applied developmental science. A current obstacle to this understanding is our reliance on programs based on one or two disciplines, which do little to promote the required trans-disciplinary breadth. If this obstacle can be overcome, the

G x E perspective provides a sophisticated framework to gain insight into mechanisms, thereby offering important prospects for translational and intervention research.

One promising avenue of investigation in that regard is the notion of *biological sensitivity to context (see Chapter 3)*, which may be thought of as a 'bell-weather' of what will unfold over the life course. The fate of children who are biologically sensitive to context has the potential to tell us whether or not our society is supporting or undermining children's prospects for positive mental health. Thus, the issue of why certain environments are associated with differing rates of negative outcomes is not simply a moral issue, but an issue that deals with human biology, trans-generational effects, and in the longer run, with society's human and social capital.

Feature 6

Early experience can alter children's trajectories through the biological embedding of early childhood experiences during sensitive periods of development and through the accumulation of damage over time. The notion that early insults may compromise children's development is not new. However, advances in developmental biology combined with mounting data from prospective longitudinal and genetically informative studies are converging on important messages regarding mechanisms of transmission and the ways in which we may be able to reduce the burden of suffering that is attributable to early experiences. A priority for future research will be to trace how early experiences 'get under the skin' to influence children's development. The possibility of epigenetic programming is a promising possibility, but one that is still in its infancy when it comes understanding developmental trajectories in humans.

Implications of feature 6 for policy and practice

Understanding the mechanisms through which early experiences may become biologically embedded and influence the future lives of children is important as it brings us closer to understanding how to protect children from pervasive and harmful experiences early in life.

Feature 7

We understand more about science and life course determinants of development than interventions.

Implications of feature 7 for policy and practice

The evidence base is clear to the extent that it demonstrates the success of intense and sustained prevention programs targeting high-risk families during the perinatal period and early childhood. Also, it shows limited evidence for the efficacy of interventions targeting families where maltreatment has already occurred. But a research agenda that would better inform policy and strategic programming is urgently needed. Many interventions that have been formally tried do not necessarily match up with the understanding of developmental science, or with the longitudinal evidence on the timing of adverse experiences that matter. The interventions for which we have high quality evidence are necessary but not sufficient; especially lacking with respect to addressing the booster systems mentioned above, as well as the community and socioeconomic determinants of developmental trajectories that lead to addictions and mental health problems. These shortcomings should frame an agenda of policy and program research for Canada and internationally.

3. Proportionate Universality

Notwithstanding the limitations in our knowledge about interventions, there is one general approach to intervention that is consistent with a goal of flattening gradients in ACE in a way that, in principle, would bring positive change to societal norms. As mentioned in the introductory chapter, this approach is known as proportionate universality: that is, programs, services, and policies that are universal, but with a scale and intensity that is proportionate to the level of disadvantage in a given context. For many years there has been a debate about the relative value and impact of universal versus targeted programs in addressing health and development issues. Universal solutions—those that are available to all children and families—are set against targeted solutions—those that are focused on special at-risk populations and in specific low-income areas. An assessment of each suggests that neither, on its own, will be sufficient in flattening substantially the social gradient. A universal approach has the potential to improve things for children in all socioeconomic ranges. But in practice, children in higher socioeconomic ranges tend to benefit more than those in lower ranges. This is because lower socioeconomic families are more likely to face obstacles to accessing services—these might be physical, cultural, or social. Using a universal approach without addressing barriers to access, one that provides the same service to all, can actually steepen the gradient, and create greater differences in child outcomes between socioeconomic ranges. Targeting programs toward children who are most vulnerable has the potential to reach children in the greatest need. But targeting also has substantial challenges. First, targeted solutions can reach the most vulnerable children in low socioeconomic ranges in a more intensive way, and so possibly improve outcomes for these children. However, as the largest number of vulnerable children is in the middle class, the majority of vulnerable children are missed. Second, targeting, by itself, does not eliminate barriers to access—barriers such as the stigma associated with some programs continue to affect families. Targeting alone then, will not flatten the social gradient overall.

A system that incorporates the principle of proportionate universality for children in their early years would create and maintain a platform of universal services organized in a way that would eliminate the barriers to access that affect populations in the highest need. In practice, this requires tailoring strategies to reach children in all walks of life and addressing the specific barriers to access that some experience. In practice, proportionate universality calls for integrating universal platforms with targeted strategies for groups with special needs and barriers.

As indicated earlier, prevention should start early if we want to alleviate or change the developmental trajectories characterizing some children. However, we do not know how to get sustained change the way that smoking was reduced by a societal level change in attitude, brought on by changing culture, opinion, and norms. After all, smoking is a discrete behaviour while parenting is an activity indivisible from daily living. A population health approach to evidence-based social change in the complex ecosystems of child development needs to be put in play here. Accordingly, this report can be seen as a piece of a larger agenda of trying to get Canadian society to commit itself to improving its prospects for healthy child development.

4. An era of experimentation in Canada

The policy and program implications of the framework articulated in this report have been detailed above; not as narrow prescriptions but, rather, suggestions for strategic avenues of approach that take into account our current best life-course, population health, and bio-psycho-social understandings. As implied by Textbox 1.1 of the Introduction, these suggestions are being made in a specific political context; one in which most of the policy and program levers and, indeed, the constitutional authority to act on family, health, and early life course issues, rests with the provinces and territories, not the Federal government. At the same time, through the Mental Health Commission of Canada, a highly relevant pan-Canadian conversation is taking place that has the capacity to promote inter-jurisdictional learning about the successes and challenges of the different policy and program mixes tried by each province and territory.

At present, policy and program mixes, from nurse home visiting to family income support, child-care and child protection, vary significantly across jurisdictions, and we expect that each jurisdiction's response to the new insights will be different. At the same time, as we have described under Feature 3 above, elements of a pan-Canadian monitoring system are already in place that, if fully implemented, would have the capacity to track the effectiveness of strategic investments early in the life course on improving outcomes in adolescence and young adulthood. Already, these monitoring data have revealed that children's rate of vulnerability in social and emotional development by school age varies more than 10-fold across several thousand Canadian neighbourhoods covering more than three-quarters of the Canadian population (Offord Centre for Child Studies). These data provide an obvious starting point for monitoring progress over time among children growing up in different circumstances, and subject to differing policy and program regimes.

Accordingly, this inter-jurisdictional diversity of approach can be made into a strength, rather than a weakness, under three conditions. First, jurisdictions agree to learn from each other and do not shy away from inter-jurisdictional comparisons; such that they are open about the nature, timing and coverage of programs and policies. Second, jurisdictions agree on standards for evaluation of outcomes and commit themselves to evidence-informed decision-making. Third, jurisdictions commit themselves to support a pan-Canadian monitoring system that can be used to track progress at the level of the population over place and time.

5. Towards a "new science" of developmental research

This report has drawn heavily upon the emerging evidence of how early experience can 'get under the skin' to influence brain and biological development. In particular, it has built upon the prospect that the environments of stimulation, support, nurturance and participation in early childhood can speak to our genes through identifiable, credible biochemical and physiological mechanisms. In turn, genes may then express themselves differently according to the quality of early experience, and do so in ways that will influence our life chances; up to and including risks of addiction and mental health problems. We believe that this epigenetic perspective, when combined with insights on life course development from birth cohort studies, and with the emerging developmental neurobiology of the brain, forms a new science. The new science has the potential to transform the way we understand the challenges raised by various developmental

health problems, including addictions and mental health problems; changing our ideas of how these problems emerge and calling into question how and when society should act to address them.

But this new science is in its infancy, leaving many foundational questions unanswered. A credible evidence base needs to be created documenting the precise nature and extent of biological embedding of specific early experiences in the epigenome and the neurobiology of the developing brain. That these processes significantly alter trajectories of human development, including addictions and mental health risks, needs to be tested though existing and new longitudinal studies; by collecting and collating information from the very beginning of the reproductive process and tracking children, families and their experiences for years and decades thereafter. Attractive concepts that have emerged from the first generation of the new science, such as biological sensitivity to context, need to be validated through strategic longitudinal and developmental neurobiology studies. Finally, the remarkable disjunction that exists between the developmental and population health approaches to the determinants of developmental health, on the one hand, and the individual-based approach to intervention, on the other, needs to be addressed in a systematic program of research and reflection.

At the present time, various elements of this multifaceted agenda are being addressed though individual research initiatives in Europe, North America, Australia and New Zealand, among others. Accordingly, we believe that the evidentiary base will continue to expand and useful new insights will continue to emerge. But the pace of knowledge generation and its relevance to Canada could be greatly enhanced by a Canadian research strategy, with secure, long-term funding. Such a strategy would include: (1) using the rich array of existing longitudinal, developmental and linked data sets in Canada, in a coordinated way, to learn more about the life course determinants of impairment in mental health in our context (see The Inventory of Pregnancy and Birth Cohort studies in Canada, SKC-ECD, MICYRN, and IHDCYH-CIHR: (Joly et al., 2012); (2) using population-based data to identify communities and regions in Canada with large, stable differences in rates of mental health problems in teenage and young adulthood. This will allow us to work backwards to understand their modifiable community and societal level determinants; (3) developing an intervention research strategy that actively incorporates population health perspectives to complex interventions in the ecology of child development, with life course and other types of prevention approaches; (4) developing responsible, state-of-the-art messaging to parents and other caregivers and a knowledge mobilization strategy that penetrates to all the geographic, socioeconomic, and ethnic communities in Canada; (5) creating opportunities to build interdisciplinary research teams that will apply the newly emerging epigenetic, brain imaging, and developmental neurobiology techniques to study the early stages of human development in socially diverse Canadian contexts.

6. A call to action

This report makes a strong case, based upon evidence from epidemiology, biology and intervention research, for focusing on the early years as a time to break the cycle linking early childhood experiences to mental health problems and unhealthy behaviours in adolescence and young adulthood. This evidence is fortuitous, because it reinforces other powerful reasons for investing in the early years. According to the United Nations Convention on the Rights of the

Child, Canada has a duty to both protect young children from adverse experiences and, also, to create the opportunity for young children's capacities to develop their potential (United Nations, 1991, 2005). In other words, Canada has committed itself both to prevent the negative and to create the positive in the early years. Next, the World Health Organization's Commission on the Social Determinants of Health (World Health Organization, 2008) made it clear that investing in the early years may be the best way to reduce health inequalities across the life course. Finally, a consensus among economists has emerged that economic returns on investment in the early years, through enhanced school success, reduced criminality, and improved well-being are, potentially, greater than any other investment in health, education, or human development that a wealthy society can make (Heckman, 2006). For all these reasons, Canadian children and their families deserve a robust strategy for tackling unhealthy behaviours and mental health through investment in the early years.

FIGURES & TEXTBOXES

Figures

Textboxes

REFERENCES

Ader, R., Felten, D. L., & Cohen, N. (2001). *Psychoneuroimmunology*. New York, NY: Academic Press.

Adler, N. E., Boyce, W. T., Chesney, M. A., Cohen, S., Folkman, S., Kahn, R. L., & Syme, S. L. (1994). Socioeconomic status and health: the challenge of the gradient. *American Psychologist, 49*(1), 15-24.

Adler, N. E., & Newman, K. (2002). Socioeconomic disparities in health: pathways and policies. *Health Affairs, 21*(2), 60-76.

Adler, N. E., & Rehkopf, D. H. (2008). U.S.disparities in health: descriptions, causes, and mechanisms. *Annual Review of Public Health, 29*, 235-252.

Afonso, V., King, S., Novakov, M., Burton, C., & Fleming, A. (2011). Accumbal dopamine function in postpartum rats that were raised without their mothers. *Hormones and Behavior*.

Afonso, V. M., Grella, S. L., Chatterjee, D., & Fleming, A. S. (2008). Previous maternal experience affects accumbal dopaminergic responses to pup-stimuli. *Brain Research, 1198*, 115-123.

Afonso, V. M., King, S., Chatterjee, D., & Fleming, A. S. (2009). Hormones that increase maternal responsiveness affect accumbal dopaminergic responses to pup- and food-stimuli in the female rat. *Hormones and Behavior, 56*(1), 11-23.

Akbari, E. M., Chatterjee, D., Levy, F., & Fleming, A. S. (2007). Experience-dependent cell survival in the maternal rat brain. *Behavioral Neuroscience, 121*(5), 1001-1011.

Alkon, A., Lippert, S., Vujan, N., Rodriquez, M. E., Boyce, W. T., & Eskenazi, B. (2006). The ontogeny of autonomic measures in 6- and 12-month-old infants. *Developmental Psychobiology, 48*(3), 197-208.

Allin, H., Wathen, C. N., & MacMillan, H. L. (2005). Treatment of child neglect: a systematic review. *Canadian Journal of Psychiatry, 50*(8), 497- 504.

Amato, P. R. (1994). Father-child relations, mother-child relations, and offspring psychological well-being in early adulthood. *Journal of Marriage and Family, 56*, 1031-1042.

American Academy of Pediatrics, & Council on Child Adolescent Health. (1998). The role of home-visitation programs in improving health outcomes for children and families. *Pediatrics, 101*(3), 486-489.

Anda, R., Felitti, V., Bremner, J., Walker, J., Whitfield, C., Perry, B., . . . Giles, W. (2006). The enduring effects of abuse and related adverse experiences in childhood: a convergence of evidence from neurobiology and epidemiology. *European Archives of Psychiatry and Clinical Neuroscience, 256*(3), 174-186.

Anda, R. F., Croft, J. B., Felitti, V. J., Nordenberg, D., Giles, W. H., Williamson, D. F., & Giovino, G. A. (1999). Adverse childhood experiences and smoking during adolescence and adulthood. *JAMA: Journal of the American Medical Association, 282*(17), 1652-1658.

Aos, S., Lieb, R., Mayfield, J., Miller, M., & Pennucci, A. (2004). Benefits and costs of prevention and early intervention programs for youth. Olympia, WA: Washington State Institute for Public Policy.

Ariès, P. (1962). *Centuries of childhood: a social history of family life*. New York, NY: Alfred A. Knopf.

Arseneault, L., Cannon, M., Fisher, H. L., Polanczyk, G., Moffitt, T. E., & Caspi, A. (2011). Childhood trauma and children's emerging psychotic symptoms: a genetically sensitive longitudinal cohort study. *American Journal of Psychiatry, 168*(1), 65-72.

Avon Longitudinal Study of Parents and Children (ALSPAC). (30 August 2012). from http://www.bristol.ac.uk/alspac/

Bachevalier, J., & Loveland, K. A. (2006). The orbitofrontal-amygdala circuit and self-regulation of social-emotional behaviour in autism. *Neuroscience and Biobehavioral Reviews, 30*(1), 91-117.

Bailey, J. A., Hill, K. G., Oesterle, S., & Hawkins, J. D. (2009). Parenting practices and problem behaviour across three generations: monitoring, harsh discipline, and drug use in the intergenerational transmission of externalizing behavior. *Developmental Psychology, 5*, 1214-1226.

Bakermans-Kranenburg, M. J., & van Ijzendoorn, M. H. (2011). Differential susceptibility to rearing environment depending on dopamine-related genes: new evidence and a meta-analysis. *Development and Psychopathology, 23*(1), 39-52.

Bakermans-Kranenburg, M. J., van Ijzendoorn, M. H., & Juffer, F. (2003). Less is more: Meta-analyses of sensitivity and attachment interventions in early childhood. *Psychological Bulletin, 129*(2), 195-215.

Bakermans-Kranenburg, M. J., Van Ijzendoorn, M. H., Mesman, J., Alink, L. R. A., & Juffer, F. (2008). Effects of an attachment-based intervention on daily cortisol moderated by dopamine receptor D4: a randomized control trial on 1-to 3-year-olds screened for externalizing behavior. *Development and Psychopathology, 20*(3), 805-820.

Bardi, M., Bode, A. E., Ramirez, S. M., & Brent, L. Y. (2005). Maternal care and development of stress responses in baboons. *American Journal of Primatology, 66*(3), 263-278.
Bardi, M., Shimizu, K., Barrett, G. M., Borgognini-Tarli, S. M., & Huffman, M. A. (2003). Peripartum sex steroid changes and maternal style in rhesus and Japanese macaques. *General and Comparative Endocrinology 133*(3), 323-331.
Bardin, J. (2012). Unlocking the brain. *Nature, 487*, 24-26.
Barker, D. J. (1990). The fetal and infant origins of adult disease. *British Medical Journal (Clinical Research Edition), 301*(6761), 1111.
Barker, D. J., Osmond, C., Forsen, T. J., Kajantie, E., & Eriksson, J. G. (2005). Trajectories of growth among children who have coronary events as adults. *New England Journal of Medicine, 353*(17), 1802-1809.
Barker, D. J. P. (1997). The fetal origins of coronary heart disease. *Acta Paediatrica Supplement, 422*, 78-92.
Barker, E., Boivin, M., Brendgen, M., Fontaine, N., Arseneault, L., Vitaro, F., & Tremblay, R. (2008). Predictive validity and early predictors of peer-victimization trajectories in preschool. *Archives of General Psychiatry, 65*(10), 1185-1192.
Barker, E. D., Copeland, W., Maughan, B., Jaffee, S. R., & Uher, R. (2012). Relative impact of maternal depression and associated risk factors on offspring psychopathology. *British Journal of Psychiatry, 200*(2), 124-129.
Barlow, J., Parsons, J., & Stewart-Brown, S. (2005). Preventing emotional and behavioural problems: the effectiveness of parenting programmes with children less than 3 years of age. *Child: Care, Health and Development, 31*(1), 33-42.
Barlow, J., Schrader - MacMillan, A., Stewart-Brown, S., Carter, Y., Sidebotham, P., & Paul, M. (2008). A systematic review of interventions for the secondary prevention and treatment of emotional abuse of children by primary carers. Coventry, UK: University of Warwick, Warwick Medical School.
Barlow, J., Simkiss, D., & Stewart-Brown, S. (2006). Interventions to prevent or ameliorate child physical abuse and neglect: findings from a systematic review of reviews. *Journal of Children's Services, 1*(3), 6-28.
Barnett, W. S., & Masse, L. N. (2007). Comparative benefit-cost analysis of the Abecedarian program and its policy implications. *Economics of Education Review, 26*(1), 113-125.
Baron, R. M., & Kenny, D. A. (1986). The moderator-mediator variable distinction in social psychological research: conceptual, strategic, and statistical considerations. *Journal of Personality and Social Psychology, 51*(6), 1173-1182.
Barr, R. G., Barr, M., Fujiwara, T., Conway, J., Catherine, N., & Brant, R. (2009a). Do educational materials change knowledge and behaviour about crying and shaken baby syndrome? A randomized controlled trial. *Canadian Medical Association Journal, 180*(19255065), 727-733.
Barr, R. G., Rivara, F. P., Barr, M., Cummings, P., Taylor, J., Lengua, L. J., & Meredith-Benitz, E. (2009b). Effectiveness of educational materials designed to change knowledge and behaviors regarding crying and shaken-baby syndrome in mothers of newborns: a randomized, controlled trial. *Pediatrics, 123*(19255028), 972-980.
Barr, R. G., Trent, R. B., & Cross, J. (2006). Age-related incidence curve of hospitalized Shaken Baby Syndrome cases: convergent evidence for crying as a trigger to shaking. *Child Abuse and Neglect, 30*(16406023), 7-16.
Barrett, J., & Fleming, A. S. (2011). Annual Research Review: All mothers are not created equal: neural and psychobiological perspectives on mothering and the importance of individual differences. *Journal of Child Psychology and Psychiatry and Allied Disciplines, 52*(4), 368-397.
Barrett, J., Wonch, K., Hall, G. B., Gonzalez, A., Ali, N., Steiner, M., & Fleming, A. S. (2011). Maternal affect and quality of parenting experiences are related to amygdala response to infant faces. *Social Neuroscience*.
Bartels, A., & Zeki, S. (2004). The neural correlates of maternal and romantic love. *Neuroimage, 21*(3), 1155-1166.
Barth, R. P. (1991). An experimental evaluation of in-home child abuse prevention services. *Child Abuse and Neglect, 15*(1959070), 363-375.
Bateson, P., Barker, D., Clutton-Brock, T., Deb, D., D'Udine, B., Foley, R. A., . . . Sultan, S. E. (2004). Developmental plasticity and human health. *Nature, 430*(6998), 419-421.
Bauer, P. M., Hanson, J. L., Pierson, R. K., Davidson, R. J., & Pollak, S. D. (2009). Cerebellar volume and cognitive functioning in children who experienced early deprivation. *Biological Psychiatry, 66*(2), 1100-1106.
Beardslee, W. R., Chien, P. L., & Bell, C. C. (2011). Prevention of mental disorders, substance abuse, and problem behaviors: a developmental perspective. *Psychiatric Services, 62*(3), 247-254.
Beauvais, C., & Jenson, J. (2003). The well-being of children: are there 'neighbourhood effects'? Ottawa, ON: Canadian Policy Research Networks.

Beebe, B., Badalamenti, A., Jaffe, J., Feldstein, S., Marquette, L., Helbraun, E., . . . Ellman, L. (2008). Distressed mothers and their infants use a less efficient timing mechanism in creating expectancies of each other's looking patterns. *Journal of Psycholinguistic Research, 37*(5), 293-307.

Belay, H., Burton, C. L., Lovic, V., Meaney, M. J., Sokolowski, M., & Fleming, A. S. (2011). Early adversity and serotonin transporter genotype interact with hippocampal glucocorticoid receptor mRNA expression, corticosterone, and behavior in adult male rats. *Behavioral Neuroscience, 125*(2), 150-160.

Belsky, J. (1997). Variation in susceptibility to environmental influence: an evolutionary argument. *Psychological Inquiry, 8*(3), 182-186.

Belsky, J., Bakermans-Kranenburg, M. J., & van Ijzendoorn, M. H. (2007). For better and for worse: differential susceptibility to environmental influences. *Current Directions in Psychological Science, 16*(6), 300-304.

Belsky, J., Conger, R., & Capaldi, D. M. (2009). The intergenerational transmission of parenting: introduction to the special section. *Developmental Psychology, 45*(5), 1201-1204.

Belsky, J., Jaffee, S. R., Sligo, J., Woodward, L., & Silva, P. A. (2005). Intergenerational transmission of warm-sensitive-stimulating parenting: a prospective study of mothers and fathers of 3-year-olds. *Child Development, 76*(2), 384-396.

Belsky, J., & Pluess, M. (2009). Beyond diathesis stress: differential susceptibility to environmental influences. *Psychological Bulletin, 135*(6), 885-908.

Belsky, J., Steinberg, L., & Draper, P. (1991). Childhood experience, interpersonal development, and reproductive strategy: and evolutionary theory of socialization. *Child Development, 62*(1935336), 647-670.

Berg, S. J., & Wynne-Edwards, K. E. (2001). Changes in testosterone, cortisol, and estradiol levels in men becoming fathers. *Mayo Clinic proceedings. Mayo Clinic, 76*(6), 582-592.

Bergman, K., Sarkar, P., Glover, V., & O'Connor, T. G. (2010). Maternal prenatal cortisol and infant cognitive development: moderation by infant-mother attachment. *Biological Psychiatry, 67*(11), 1026-1032.

Bernard, K., Butzin-Dozier, Z., Rittenhouse, J., & Dozier, M. (2010). Cortisol production patterns in young children living with birth parents vs children placed in foster care following involvement of child protective services. *Archives of Pediatrics and Adolescent Medicine, 164*(5), 438-443.

Bernet, C. Z., & Stein, M. B. (1999). Relationshp of childhoof maltreatment to the onset and course of major depression in adulthood. *Depression and Anxiety, 9*(4), 169-174.

Bernstein, I. H., Rush, A. J., Yonkers, K., Carmody, T. J., Woo, A., McConnell, K., & Trivedi, M. H. (2008). Symptom features of postpartum depression: are they distinct? *Depression and Anxiety, 25*(1), 20-26.

Berridge, K. C., & Robinson, T. E. (1998). What is the role of dopamine in reward: hedonic impact, reward learning, or incentive salience? *Brain Research. Brain Research Reviews, 28*(3), 309-369.

Bifulco, A., Kwon, J., Jacobs, C., Moran, P. M., Bunn, A., & Beer, N. (2006). Adult attachment styles as mediator between childhood neglect/abuse and adult depression and anxiety. *Social psychiatry and psychiatric epidemiology, 41*(10), 796-805.

Bifulco, A., Moran, P. M., Baines, R., Bunn, A., & Stanford, K. (2002). Exploring psychological abuse in childhood: II. Association with other abuse and adult clinical depression. *Bulletin of the Menninger Clinic, 66*(3), 241-258.

Bilukha, O., Hahn, R. A., Crosby, A., Fullilove, M. T., Liberman, A., Moscicki, E., . . . Briss, P. A. (2005). The effectiveness of early childhood home visitation in preventing violence: a systematic review. *American Journal of Preventive Medicine, 28*(15698746), 11-39.

Bird, A. (2007). Perceptions of epigenetics. *Nature, 447*(7143), 396-398.

Blumenshine, P., Egerter, S., Barclay, C. J., Cubbin, C., & Braveman, P. A. (2010). Socioeconomic disparities in adverse birth outcomes: a systematic review. *American Journal of Preventive Medicine, 39*(3), 263-272.

Boisjoli, R., Vitaro, F., Lacourse, E., Barker, E. D., & Tremblay, R. E. (2007). Impact and clinical significance of a preventive intervention for disruptive boys: 15-year follow-up. *British Journal of Psychiatry, 191*, 415-419.

Boivin, M., Brendgen, M., Dionne, G., Dubois, L., Pérusse, D., Robay, P., Tremblay, R.E. & Vitaro, F. (in press). The Quebec Newborn Twin Study into adolescence: 15 years later. *Twin Research and Human Genetics.*

Boivin, M., Brendgen, M., Vitaro, F., Dionne, G., Girard, A., Pérusse, D., & Tremblay, R. E. (in press-b). Strong genetic contribution to peer relation difficulties at school entry: findings from a kongitudinal twin study. *Child Development*.

Boivin, M., Perusse, D., Dionne, G., Saysset, V., Zocolillo, M., Tarabulsy, G. M., . . . Tremblay, R. E. (2005). The genetic-environmental etiology of parents' perceptions and self-assessed behaviours toward their 5-month-old infants in a large twin and singleton sample. *Journal of Child Psychology and Psychiatry and Allied Disciplines, 46*(6), 612-630.

Bollati, V., & Baccarelli, A. (2010). Environmental epigenetics. *Heredity, 105*(1), 105-112.

Bornstein, M. H. (1995). *Handbook of parenting: Biology and ecology of parenting* (Vol. 2). Mahwat, NJ: Lawrence Erlbaum & Associates.
Bornstein, M. H., Tamis-Lemonda, C. S., Hahn, C., & Haynes, O. M. (2008). Maternal responsiveness to young children at three ages: longitudinal analysis of a multi-dimensional, modular, and specific parenting construct. *Developmental Psychology, 44*(3), 867-874.
Bos, K. J., Fox, N., Zeanah, C. H., & Nelson, C. A. (2009). Effects of early psychosocial deprivation on the development of memory and executive function. *Frontiers in Behavioral Neuroscience, 3*, 16.
Boyce, P. M., & Todd, A. L. (1992). Increased risk of postnatal depression after emergency caesarean section. *Medical Journal of Australia, 157*(3), 172-174.
Boyce, W. T., Chesney, M., Alkon-Leonard, A., Tschann, J., Adams, S., Chesterman, B., . . . Wara, D. (1995). Psychobiologic reactivity to stress and childhood respiratory illnesses: results of two prospective studies. *Psychosomatic Medicine, 57*, 411-422.
Boyce, W. T., Chesterman, E. A., Martin, N., Folkman, S., Cohen, F., & Wara, D. (1993). Immunologic changes occurring at kindergarten entry predict respiratory illnesses following the Loma Prieta earthquake. *Journal of Developmental and Behavioral Pediatrics, 14*(5), 296-303.
Boyce, W. T., Den Besten, P. K., Stamperdahl, J., Zhan, L., Jiang, Y., Adler, N. E., & Featherstone, J. D. (2010). Social inequalities in childhood dental caries: the convergent roles of stress, bacteria and disadvantage. *Social Science and Medicine, 71*(9), 1644-1652.
Boyce, W. T., & Ellis, B. J. (2005). Biological sensitivity to context: I.An evolutionary-developmental theory of the origins and functions of stress reactivity. *Development and Psychopathology, 17*(2), 271-301.
Boyden, J., & Levison, D. (2000). Children as economic and social actors in the development process *Expert Group on Development Issues*. Stockholm, Sweden: Government of Sweden.
Bradley, R. G., Binder, E. B., Epstein, M. P., Tang, Y., Nair, H. P., Liu, W., . . . Ressler, K. J. (2008). Influence of child abuse on adult depression: moderation by the corticotropin-releasing hormone receptor gene. *Archives of General Psychiatry, 65*(2), 190-200.
Bradley, R. H., & Corwyn, R. F. (2002). Socioeconomic status and child development. *Annual Review of Psychology, 53*, 371-399.
Brand, S. R., & Brennan, P. A. (2009). Impact of antenatal and postpartum maternal mental illness: how are the children? *Clinical Obstetrics and Gynecology, 52*(3), 441-455.
Brayden, R. M., Maclean, W. E., Bonfiglio, J. F., & Altemeier, W. (1993). Behavioral antecedents of pediatric poisonings. *Clinical Pediatrics, 32*(1), 30- 35.
Brendgen, M., Vitaro, F., Boivin, M., Dionne, G., & Perusse, D. (2006). Examining genetic and environmental effects on reactive versus proactive aggression. *Developmental Psychology, 42*(6), 1299-1312.
Brezo, J., Barker, E., Paris, J., Hebert, M., Vitaro, F., Tremblay, R., & Turecki, G. . (2008a). Childhood trajectories of anxiousness and disruptiveness as predictors of suicide attempts. *Archives of Pediatrics and Adolescent Medicine, 162*(11), 1015-1021.
Brezo, J., Bureau, A., Mérette, C., Jomphe, V., Barker, E. D., Vitaro, F., . . . Turecki, G. (2010). Differences and similarities in the serotonergic diathesis for suicide attempts and mood disorders: a 22-year longitudinal gene-environment study. *Molecular Psychiatry, 15*(8), 831-843.
Brezo, J., Paris, J., Hébert, M., Vitaro, F., Tremblay, R., & Turecki, G. (2008b). Broad and narrow personality traits as markers of one-time and repeated suicide attempts: a population-based study. *BMC Psychiatry, 8*, 15.
Britner, P. A., & Reppucci, N. D. (1997). Prevention of child maltreatment: Evaluation of a parent education program for teen mothers. *Journal of Child and Family Studies, 6*(2), 165-175.
Broidy, L. M., Nagin, D. S., Tremblay, R. E., Bates, J. E., Brame, B., Dodge, K. A., & Vitaro, F. (2003). Developmental trajectories of childhood disruptive behaviors and adolescent delinquency: a six-site, cross-national study. *Developmental Psychology, 39*(2), 222-245.
Bronfenbrenner, U. (1979). *The ecology of human development: experiments by nature and design*. Cambridge, MA: Harvard University Press.
Bronfenbrenner, U., & Ceci, S. J. (1994). Nature-nurture reconceptualized in developmental perspective: a bioecological model. *Psychological Review, 101*(4), 568-586.
Bronfenbrenner, U., & Evans, G. W. (2000). Developmental science in the 21st century: emerging questions, theoretical models, research designs and empirical findings. *Social Development, 9*(1), 115-125.
Brown, D. W., Anda, R. F., Tiemeier, H., Felitti, V. J., Edwards, V. J., Croft, J. B., & Giles, W. H. (2009). Adverse childhood experiences and the risk of premature mortality. *American Journal of Preventive Medicine, 37*(5), 389-396.

Brown, G. W., & Moran, P. (1994). Clinical and psychosocial origins of chronic depressive episodes. I: a community survey. *British Journal of Psychiatry, 165*(4), 447-456.
Brown, J., Cohen, P., Johnson, J. G., & Smailes, E. M. (1999). Childhood abuse and neglect: specificity of effects on adolescent and young adult depression and suicidality. *Journal of the American Academy of Child and Adolescent Psychiatry, 38*(12), 1490-1496.
Brown, R. L. (2010). Epidemiology of injury and the impact of health disparities. *Current Opinion in Pediatrics, 22*(3), 321-325.
Brummelte, S., & Galea, L. A. (2010). Chronic corticosterone during pregnancy and postpartum affects maternal care, cell proliferation and depressive-like behavior in the dam. *Hormones and Behavior, 58*(5), 769-779.
Brunk, M., Henggeler, S. W., & Whelan, J. P. (1987). Comparison of multisystemic therapy and parent training in the brief treatment of child abuse and neglect. *Journal of Consulting and Clinical Psychology, 55*(3571669), 171-178.
Bull, J., McCormick, G., Swann, C., & Mulvihill, C. (2004). Ante- and post- natal home-visiting programs: a review of reviews: evidence briefing. London, UK: NHS Health Development Agency.
Burchinal, M. R., Campbell, F. A., Bryant, D. M., Wasik, B. H., & Ramey, C. T. (1997). Early intervention and mediating processes in cognitive performance of children of low-income African American families. *Child Development, 68*(5), 935-954.
Burton, C., Lovic, V., & Fleming, A. S. (2006). Early adversity alters attention and locomotion in adult Sprague-Dawley rats. *Behavioral Neuroscience, 120*(3), 665-675.
Burton, C. L., Chatterjee, D., Chatterjee-Chakraborty, M., Lovic, V., Grella, S. L., Steiner, M., & Fleming, A. S. (2007). Prenatal restraint stress and motherless rearing disrupts expression of plasticity markers and stress-induced corticosterone release in adult female Sprague-Dawley rats. *Brain Research, 1158*, 28-38.
Buss, C., Lord, C., Wadiwalla, M., Hellhammer, D. H., Lupien, S. J., Meaney, M. J., & Pruessner, J. C. (2007). Maternal care modulates the relationship between prenatal risk and hippocampal volume in women but not in men. *Journal of Neuroscience, 27*(10), 2592-2595.
Butler-Jones, D. (2011). The Chief Public Health Officer's report on the state of public health in Canada, 2011: youth and young adults – Life in transition. Ottawa, ON: Public Health Agency of Canada.
Bybee, D., & Sullivan, C. M. (2005). Predicting re-victimization of battered women 3 years after exiting a shelter program. *American Journal of Community Psychology, 36*(16134046), 85-96.
Cacioppo, J. T. (1994). Social neuroscience: autonomic, neuroendocrine, and immune responses to stress. *Psychophysiology, 31*(2), 113-128.
Cacioppo, J. T., Berntson, G. G., Sheridan, J. F., & McClintock, M. K. (2000). Multilevel integrative analyses of human behavior: Social neuroscience and the complementing nature of social and biological approaches. *Psychological Bulletin, 126*(6), 829-843.
Cacioppo, J. T., Tassinary, L. G., & Berntson, G. G. (Eds.). (2000). *Handbook of psychophysiology*. Cambridge, MA: Cambridge University Press.
Cadoret, R. J., Troughton, E., & O'Gorman, T. W. (1987). Genetic and environmental factors in alcohol abuse and antisocial personality. *Journal of Studies on Alcohol, 48*(1), 1-8.
Caldera, D., Burrell, L., Rodriguez, K., Crowne, S. S., Rohde, C., & Duggan, A. (2007). Impact of a statewide home visiting program on parenting and on child health and development. *Child Abuse Negl, 31*(17822765), 829-852.
Caldji, C., Diorio, J., & Meaney, M. J. (2003). Variations in maternal care alter GABA(A) receptor subunit expression in brain regions associated with fear. *Neuropsychopharmacology, 28*(11), 1950-1959.
Campaign 2000. (2010). 2010 report card on child and family poverty in Canada: 1989 – 2010. from http://www.campaign2000.ca/
Campbell, F. A., Ramey, C. T., Pungello, E., Sparling, J., & Miller-Johnson, S. (2002). Early childhood education: young adult outcomes from the Abecedarian Project. *Applied Developmental Science, 6*(1), 42-57.
Canadian Institute for Health Information. (2005). Improving the health of young Canadians. Ottawa, ON: CIHI.
Canadian Institutes of Health Research. (2009). Inventory of pregnancy and birth cohort studies in Canada - December 2009. from http://www.cihr-irsc.gc.ca/e/40753.html
Casey, B. J., Glatt, C. E., Tottenham, N., Soliman, F., Bath, K., Amso, D., . . . Lee, F. S. (2009). Brain-derived neurotrophic factor as a model system for examining gene by environment interactions across development. *Neuroscience, 164*(1), 108-120.
Caspi, A., McClay, J., Moffitt, T. E., Mill, J., Martin, J., Craig, I. W., . . . Poulton, R. (2002). Role of genotype in the cycle of violence in maltreated children. *Science, 297*(5582), 851-854.

Caspi, A., Sugden, K., Moffitt, T. E., Taylor, A., Craig, I. W., Harrington, H., . . . Poulton, R. (2003). Influence of life stress on depression: moderation by a polymorphism in the 5-HTT gene. *Science, 301*(5631), 386-389.
Cassel, J. (1976). The contribution of the social environment to host resistance. *American Journal of Epidemiology, 104*, 107-123.
CEDAW. (1980). Convention on the Eliminatiom of all forms of Discrimination Against Women. New York, NY: United Nations General Assembly.
Centers for Disease Control and Prevention. (June 1, 2011). Adverse Childhood Experiences (ACE) Study. from http://www.cdc.gov/ace/index.htm
Chaffin, M., Hecht, D., Bard, D., Silovsky, J. F., & Beasley, W. H. (2012). A statewide trial of the SafeCare home-based services model with parents in Child Protective Services. *Pediatrics, 129*(3), 509-515.
Chaffin, M., Silovsky, J. F., Funderburk, B., Valle, L. A., Brestan, E. V., Balachova, T., . . . Bonner, B. L. (2004). Parent-child interaction therapy with physically abusive parents: efficacy for reducing future abuse reports. *Journal of Consulting and Clinical Psychology, 72*(15279533), 500-510.
Chambless, D. L., Baker, M. J., Baucom, D. H., Beutler, L. E., Calhoun, K. S., Crits-Christoph, P., . . . Woody, S. R. (1998). Update on empirically validated therapies, II. *Clinical Psychologist, 51*(1), 3-16.
Champagne, F., & Meaney, M. J. (2001). Like mother, like daughter: evidence for non-genomic transmission of parental behavior and stress responsivity. *Progress in Brain Research, 133*, 287-302.
Champagne, F. A. (2010). Early adversity and developmental outcomes: Interaction between genetics, epigenetics, and social experiences across the life span. *Perspectives on Psychological Science, 5*(5), 564.
Champagne, F. A., Chretien, P., Stevensson, C. W., Zhang, T. Y., Gratton, A., & Meaney, M. J. (2004). Variations in nucleus accumbens dopamine associated with individual differences in maternal behavior in the rat. *Journal of Neuroscience, 24*(17), 4113-4123.
Champagne, F. A., Francis, D. D., Mar, A., & Meaney, M. J. (2003). Variations in maternal care in the rat as a mediating influence for the effects of environment and development. *Physiology & Behavior, 79*, 359-371.
Champagne, F. A., & Meaney, M. J. (2006). Stress during gestation alters postpartum maternal care and the development of the offspring in a rodent model. *Biological Psychiatry, 59*(12), 1227-1235.
Champoux, M., Bennett, A., Shannon, C., Higley, J. D., Lesch, K. P., & Suomi, S. J. (2002). Serotonin transporter gene polymorphism, differential early rearing, and behavior in rhesus monkey neonates. *Molecular Psychiatry, 7*(10), 1058-1063.
Chang, L., Schwartz, D., Dodge, K. A., & McBride-Chang, C. (2003). Harsh parenting in relation to child emotion regulation and aggression. *Journal of Family Psychology, 17*(4), 598-606.
Chatterjee-Chakraborty, M., & Chatterjee, D. (2010). Aritificial rearing inhibits apoptotic cell death through action on pro-apoptotic signalling molecules during brain development: replacement licking partially reverses these effects. *Brain Research, 1348*, 10-20.
Chatterjee, D., Chatterjee-Chakraborty, M., Rees, S., Cauchi, J., de Medeiros, C. B., & Fleming, A. S. (2007). Maternal isolation alters the expression of neural proteins during development: 'Stroking' stimulation reverses these effects. *Brain Research, 1158*, 11-27.
Chaudron, L. H., Kitzman, H. J., Peifer, K. L., Morrow, S., Perez, L. M., & Newman, M. C. (2005). Prevalence of maternal depressive symptoms in low-income Hispanic women. *Journal of Clinical Psychiatry, 66*(4), 418-420.
Chen, E., Matthews, K. A., & Boyce, W. T. (2002). Socioeconomic differences in children's health: how and why do these relationships change with age? *Psychological Bulletin, 128*(2), 295-329.
Chen, O. S., & Kaplan, J. (2001a). YFH1 mediated iron homeostasis is independent of mitochondrial respiration. *FEBS Letters, 509*(1), 131-134.
Chen, Z.-y., & Kaplan, H. B. (2001b). Intergenerational transmission of constructive parenting. *Journal of Marriage and Family, 63*(1), 17-31.
Chen, Z. Y., Liu, R. X., & Kaplan, H. B. (2008). Mediating mechanisms for the intergenerational transmission of constructive parenting: A prospective longitudinal study. *Journal of Family Issues, 29*(12), 1574-1599.
Chico, E., Gonzalez, A., Wonch, K., & Fleming, A. S. (2010). *Sensitive mothering requires good executive function: Challenges faced by teenage mothers*. Paper presented at the Society for behavioral neuroendocrinology 14th annual meeting. Poster schedule.
Child Welfare Information Gateway. Preventing child abuse & neglect. Retrieved May 12, 2012, from http://www.childwelfare.gov/
Christian, C. W., & Block, R. (2009). Abusive head trauma in infants and children. *Pediatrics, 123*(19403508), 1409-1411.

Chrousos, G. P. (1998). Stressors, stress, and neuroendocrine integration of the adaptive response. The 1997 Hans Selye Memorial Lecture. *Annals of the New York Academy of Sciences, 851*(1 Spec No), 311-335.

CHU Sainte-Justine Research Center, & Clinical Research Unit on Children's Psychosocial Maladjustment. The Quebec Longitudinal Study of Kindergarten Children (QLSKC). Retrieved 30 August, 2012, from http://www.chu-sainte-justine.org/research/projetsRC.aspx?ID_ProjetRC=3114&id_menu=2321

Chung, E. K., McCollum, K. F., Elo, I. T., Lee, H. J., & Culhane, J. F. (2004). Maternal depressive symptoms and infant helath practices among low-income women. *Pediatrics, 113*(6), 523-529.

Cicchetti, D., Rogosch, F. A., & Toth, S. L. (1998). Maternal depressive disorder and contextual risk: contributions to the development of attachment insecurity and behavior problems in toddlerhood. *Development and Psychopathology, 10*(2), 283-300.

Clark, C., Caldwell, T., Power, C., & Stansfeld, S. A. (2010). Does the influence of childhood adversity on psychopathology persist across the lifecourse? A 45-year prospective epidemiologic study. *Annals of Epidemiology, 20*(20382340), 385-394.

Cloninger, C., Martin, R. L., Guze, S. B., & Clayton, P. J. (1985). Current status of schizophrenia as a disease concept. In M. Alpert (Ed.), *Controversies in schizophrenia: Changes and constancies: Proceedings of the 74th Annual Meeting of the American Psychopathological Association, New York City, March 1-3, 1984* (pp. 12-24). New York, NY: Guilford Press.

Cohen, J. A., Deblinger, E., Mannarino, A. P., & Steer, R. A. (2004). A multisite, randomized controlled trial for children with sexual abuse-related PTSD symptoms. *Journal of the American Academy of Child and Adolescent Psychiatry, 43*(15187799), 393-402.

Cohen, J. A., Mannarinoa, A. P., & Murray, L. K. (2011). Trauma-focused CBT for youth who experience ongoing traumas. *Child Abuse and Neglect, 35*(8), 637-646

Cohen, S., Janicki-Deverts, D., Chen, E., & Matthews, K. A. (2010). Childhood socioeconomic status and adult health. *Annals of the New York Academy of Sciences, 1186*, 37-55.

Cohen, S., Line, S., Manuck, S. B., Rabin, B. S., Heise, E. R., & Kaplan, J. R. (1997). Chronic social stress, social status, and susceptibility to upper respiratory infections in nonhuman primates [see comments]. *Psychosomatic Medicine, 59*(3), 213-221.

Cohen, S., Miller, G. E., & Rabin, B. S. (2001). Psychological stress and antibody response to immunization: a critical review of the human literature. *Psychosomatic Medicine, 63*(1), 7-18.

Cohen, S., Tyrrell, D. A. J., & Smith, A. P. (1991). Psychological stress and susceptibility to the common cold. *New England Journal of Medicine, 325*, 606-612.

Cohen, S., & Williamson, G. M. (1991). Stress and infectious disease in humans. *Psychological Bulletin, 109*(1), 5-24.

Colborn, T. (2004). Neurodevelopment and endocrine disruption. *Environmental Health Perspectives, 112*(9), 944-949.

Coleman, J. S. (1988). Social capital in the creation of human capital. *American Journal of Sociology, 94*(Suppl - Organizations and Institutions: Sociological and Economic Approaches to the Analysis of Social Structure), S95-S120.

Colley, J. R., Douglas, J. W., & Reid, D. D. (1973). Respiratory disease in young adults: influence of early childhood lower respiratory tract illness, social class, air pollution, and smoking. *British Medical Journal (Clinical Research Edition), 3*(5873), 195-198.

Collishaw, S., Dunn, J., O'Connor, T. G., & Golding, J. (2007). Maternal childhood abuse and offspring adjustment over time. *Development and Psychopathology, 19*(2), 367-383.

Conger, R. D., Belsky, J., & Capaldi, D. M. (2009). The intergenerational transmission of parenting: closing comments for the special section. *Developmental Psychology, 45*(5), 1276-1283.

Conger, R. D., Conger, K. J., Elder, G. H., Lorenz, F. O., Simons, R. L., & Whitbeck, L. B. (1992). A family process model of economic hardship and adjustment of early adolescent boys. *Child Development, 63*(3), 526-541.

Conger, R. D., Neppl, T. K., Kim, K. J., & Scaramella, L. V. (2003). Angry and aggressive behaviour across three generations: a prospective, longitudinal study of parents and children. *Journal of Abnormal Child Psychology, 31*(2), 143-160.

Connell, A. M., & Goodman, S. H. (2002). The association between psychopathology in fathers versus mothers and children's internalizing and externalizing behavior problems: a meta-analysis. *Psychological Bulletin, 128*(5), 746-773.

Cooper, P. J., & Murray, L. (1995). Course and recurrence of postnatal depression. Evidence for the specificity of the diagnostic concept. *British Journal of Psychiatry, 166*(2), 191-195.

Coplan, J. D., Pine, D., Papp, L., Martinez, J., Cooper, T., Rosenblum, L. A., & Gorman, J. M. (1995). Uncoupling of the nonadrenergic-hypothalamic-pituitary-adrenal axis in panic disorder patients. *Neuropsychopharmacology, 13*(1), 65-73.

Corter, C., & Fleming, A. S. (2002). Psychobiology of maternal behavior in human beings. In M. Bomstein (Ed.), *Handbook of parenting* (2nd ed.). Mahwah, NJ: Lawrence Erlbaum.

Costello, E. J., Compton, S. N., Keeler, G., & Angold, A. (2003). Relationships between poverty and psychopathology: a natural experiment. *JAMA: Journal of the American Medical Association, 290*(15), 2023-2029.

Côté, S., Zoccolillo, M., Tremblay, R. E., Nagin, D., & Vitaro, F. (2001). Predicting girls' conduct disorder in adolescence from childhood trajectories of disruptive behaviors. *Journal of the American Academy of Child and Adolescent Psychiatry, 40*(6), 678-684.

Côté, S. M., Boivin, M., Liu, X., Nagin, D. S., Zoccolillo, M., & Tremblay, R. E. (2009). Depression and anxiety symptoms: onset, developmental course and risk factors during early childhood. *Journal of Child Psychology and Psychiatry and Allied Disciplines, 50*(10), 1201-1208.

Côté, S. M., Boivin, M., Nagin, D. S., Japel, C., Xu, Q., Zoccolillo, M., . . . Tremblay, R. E. (2007). The role of maternal education and nonmaternal care services in the prevention of children's physical aggression problems. *Archives of General Psychiatry, 64*(11), 1305-1312.

Côté, S. M., Pingault, J.-B., Boivin, M., Japel, C., Nagin, D. S., Xu, Q., . . . Tremblay, R. E. (2010). Pre-school education services and aggressive behaviour: a preventive role in vulnerable families. *PSN. Psychiatrie, Sciences Humaines, Neurosciences, 8*(2), 77-87.

Cottrell, E. C., & Seckl, J. R. (2009). Prenatal stress, glucocorticoids and the programming of adult disease. *Frontiers in Behavioral Neuroscience, 3*(19).

Courtney, M. E. (1995). Reentry to foster care of children returned to their families. *Social Service Review, 69*(2), 226-241.

Cox, J. L., Murray, D., & Chapman, G. (1993). A controlled study of the onset, duration and prevalence of postnatal depression. *British Journal of Psychiatry, 163*, 27-31.

Culp, R. E., Little, V., Letts, D., & Lawrence, H. (1991). Maltreated children's self-concept: effects of a comprehensive treatment program. *American Journal of Orthopsychiatry, 61*(2006667), 114-121.

Curley, K. O. J., Neurendorff, D. A., Lewis, A. W., Rouguette, F. M., Jr., Randel, R. D., & Welsh, T. H. J. (2010). The effectiveness of vasopression as an ACTH secretagogue in cattle differs with temperament. *Physiology and Behavior, 101*(5), 699-704.

Currie, J., & Tekin, E. (2006). Does child abuse cause crime? NBER Working Paper No. 12171. Cambridge, MA: National Bureau of Economic Research.

D'Angiulli, A., Herdman, A., Stapells, D., & Hertzman, C. (2008). Children's event-related potentials of auditory selective attention vary with their socioeconomic status. *Neuropsychology, 22*(3), 293-300.

Danese, A. (2009). Adverse childhood experiences and adult risk factors for age-related disease: depression, inflammation, and clustering of metabolic risk markers. *Archives of Pediatrics and Adolescent Medicine, 163*(12), 1072-4710.

Davey Smith, G., & Lynch, J. (2004). Life course approaches to socioeconomic differentials in health. In D. Kuh & Y. Ben-Shlomo (Eds.), *A life course approach to chronic disease epidemiology* (2nd ed.). Oxford, England: Oxford University Press.

Davis, M. K., & Gidycz, C. A. (2000). Child sexual abuse prevention programs: a meta-analysis. *Journal of Clinical Child and Adolescent Psychology, 29*(10802834), 257-265.

Davis, R. N., Davis, M. M., Freed, G. L., & Clark, S. J. (2011). Fathers' depression related to positive and negative parenting behaviors with 1-year-old children. *Pediatrics, 127*(4), 612-618.

De Bellis, M. D. (2005). The psychobiology of neglect. *Child Maltreatment, 10*(2), 150-172.

de Paul, J., & Domenech, J. (2000). Childhood history of abuse and child abuse potential in adolescent mothers: a longitudinal study. *Child Abuse and Neglect, 24*(5), 701-713.

Deblinger, E., Lippmann, J., & Steer, R. (1996). Sexually abused children suffering posttraumatic stress symptoms: initial treatment outcome findings. *Child Maltreatment, 1*(4), 310-321

Deblinger, E., Steer, R. A., & Lippmann, J. (1999). Two-year follow-up study of cognitive behavioral therapy for sexually abused children suffering post-traumatic stress symptoms. *Child Abuse and Neglect, 23*(12), 1371–1378.

Delahunty, K. M., McKay, D. W., Noseworthy, D. E., & Storey, A. E. (2007). Prolactin responses to infant cues in men and women: effects of parental experience and recent infant contact. *Hormones and Behavior, 51*(2), 213-220.

DePanfilis, D., & Zuravin, S. J. (1999). Epidemiology of child maltreatment recurrences. *Social Service Review, 73*(2), 218-239.
DeRijk, R., & de Kloet, R. E. (2005). Corticosteroid receptor genetic polymorphisms and stress responsivity. *Endocrine, 28*(3), 263-269.
Dias, M. S., Smith, K., DeGuehery, K., Mazur, P., Li, V., & Shaffer, M. L. (2005). Preventing abusive head trauma among infants and young children: a hospital-based, parent education program. *Pediatrics, 115*(15805350), 470-477.
Diego, M. A., Field, T., Hernandez-Reif, M., Cullen, C., Schanberg, S., & Kuhn, C. (2004). Prepartum, postpartum, and chronic depression effects on newborns. *Psychiatry, 67*(1), 63-80.
Diego, M. A., Field, T., Jones, N. A., & Hernadez-Reif, M. (2006). Withdrawn and intrusive maternal interaction style and infant frontal EEG asymmetry shifts in infants of depressed and non-depressed mothers. *Infant Behavior and Development, 29*(2), 220-229.
Diego, M. A., Jones, N. A., & Field, T. (2010). EEG in 1-week, 1-month and 3-month-old infants of depressed and non-depressed mothers. *Biological Psychology, 83*(1), 7-14.
Dillon, D. G., Holmes, A. J., Birk, J. L., Brooks, N., Lyons-Ruth, K., & Pizzagalli, D. A. (2009). Childhood adversity is associated with left basal ganglia dysfunction during reward anticipation in adulthood. *Biological Psychiatry, 66*(3), 206-213.
Dionne, G., Tremblay, R., Boivin, M., Laplante, D., & Pérusse, D. (2003). Physical aggression and expressive vocabulary in 19-month-old twins. *Developmental Psychology, 39*(2), 261-273.
DiPietro, J. A. (2000). Baby and the brain: advances in child development. *Annual Review of Public Health, 21*, 455-471.
Dix, T. (1991). The affective organization of parenting - Adaptive and maladaptative processes. *Psychological Bulletin, 110*(1), 3-25.
Dobkin, P. L., Tremblay, R. E., Mâsse, L. C., & Vitaro, F. (1995). Individual and peer characteristics in predicting boys' early onset of substance abuse: a seven-year longitudinal study. *Child Development, 66*(4), 1198-1214.
Dong, M., Giles, W. H., Felitti, V. J., Dube, S. R., Williams, J. E., Chapman, D. P., & Anda, R. F. (2004). Insights into causal pathways for ischemic heart disease: adverse childhood experiences study. *Circulation, 110*(13), 1761-1766.
Dowd, J. B., Zajacova, A., & Aiello, A. (2009). Early origins of health disparities: burden of infection, health, and socioeconomic status in U.S. children. *Social Science and Medicine, 68*(4), 699-707.
Doyle, J. J. J. (2007). Child protection and child outcomes: Measuring the effects of foster care. *American Economic Review, 97*(5), 1583-1610.
Drake, B., Jonson-Reid, M., & Sapokaite, L. (2006). Re-reporting of child maltreatment: does participation in other public sector services moderate the likelihood of a second maltreatment report? *Child Abuse and Neglect, 30*(17112587), 1201-1226.
Drukker, M., Kaplan, C., Schneiders, J., Feron, F., & van Os, J. (2006). The wider social environment and changes in self-reported quality of life in the transition from late childhood to early adolescence: a cohort study. *BMC Public Health, 6*(1), 1-11.
Dube, S. R., Anda, R. F., Felitti, V. J., Chapman, D. P., Williamson, D. F., & Giles, W. H. (2001). Childhood abuse, household dysfunction, and the risk of attempted suicide throughout the life span - Findings from the Adverse Childhood Experiences Study. *JAMA - Journal of the American Medical Association, 286*(24), 3089-3096.
Dube, S. R., Anda, R. F., Felitti, V. J., Edwards, V. J., & Croft, J. B. (2002). Adverse childhood experiences and personal alcohol abuse as an adult. *Addictive Behaviors, 27*(5), 713-725.
Dube, S. R., Anda, R. F., Whitfield, C. L., Brown, D. W., Felitti, V., Dong, M. X., & Giles, W. H. (2005). Long-term consequences of childhood sexual abuse by gender of victim. *American Journal of Preventive Medicine, 28*(5), 430-438.
Dube, S. R., Felitti, V. J., Dong, M., Chapman, D. P., Giles, W. H., & Anda, R. F. (2003). Childhood abuse, neglect, and household dysfunction and the risk of illicit drug use: the Adverse Childhood Experiences Study. *Pediatrics, 111*(3), 564-572.
Dubos, R., Savage, D., & Schaedler, R. (1966). Biological Freudianism. Lasting effects of early environmental influences. *Pediatrics, 38*(5), 789-800.
Dubowitz, H., Feigelman, S., Lane, W., & Kim, J. (2009). Pediatric primary care to help prevent child maltreatment: the Safe Environment for Every Kid (SEEK) Model. *Pediatrics, 123*(19255014), 858-864.

Duggan, A., Caldera, D., Rodriguez, K., Burrell, L., Rohde, C., & Crowne, S. S. (2007). Impact of a statewide home visiting program to prevent child abuse. *Child Abuse and Neglect, 31*(8), 801-827.
Duggan, A., Fuddy, L., Burrell, L., Higman, S. M., McFarlane, E., Windham, A., & Sia, C. (2004). Randomized trial of a statewide home visiting program to prevent child abuse: impact in reducing parental risk factors. *Child Abuse and Neglect, 28*(6), 625-645.
Duggan, A. K., McFarlane, E. C., Windham, A. M., Rohde, C. A., Salkever, D. S., Fuddy, L., . . . Sia, C. C. (1999). Evaluation of Hawaii's Healthy Start Program. *Future of Children, 9*(10414011), 66-90.
Duncan, G. J., Brooks-Gunn, J., & Klebanov, P. K. (1994). Economic deprivation and early childhood development. *Child Development, 65*(2), 296-318.
Dunedin Multidisciplinary Health and Development Research Unit. Welcome to the Dunedin Multidisciplinary Health and Development Research Unit (DMHDRU). Retrieved August 30, 2012, from http://dunedinstudy.otago.ac.nz/
Dunn, J. R., & Hayes, M. V. (2000). Social inequality, population health, and housing: a study of two Vancouver neighborhoods. *Social Science and Medicine, 51*(4), 563-587.
Duric, V., Banasr, M., Licznerski, P., Schmidt, H. D., Stockmeier, C. A., Simen, A. A., . . . Duman, R. S. (2010). A negative regulator of MAP kinase causes depressive behavior. *Nature Medicine, 16*(11), 1328-1332.
Eckenrode, J., Campa, M., Luckey, D. W., Henderson Jr, C. R., Cole, R., Kitzman, H., . . . Olds, D. (2010). Long-term effects of prenatal and infancy nurse home visitation on the life course of youths: 19-year follow-up of a randomized trial. *Archives of Pediatrics and Adolescent Medicine, 164*(1), 9-15.
Edwards, V. J., Holden, G. W., Felitti, V. J., & Anda, R. F. (2003). Relationship between multiple forms of childhood maltreatment and adult mental health in community respondents: results from the adverse childhood experiences study. *American Journal of Psychiatry, 160*(8), 1453-1460.
Eigsti, I.-M., & Cicchetti, D. (2004). The impact of child maltreatment on expressive syntax at 60 months. *Developmental Science, 7*(1), 88-102.
Ellis, B., Jackson, J., & Boyce, W. (2006). The stress response systems: universality and adaptive individual differences. *Developmental Review, 26*(2), 175-212.
Ellis, B. J. (2004). Timing of pubertal maturation in girls: an integrated life history approach. *Psychological Bulletin, 130*(15535743), 920-958.
Ellis, B. J., & Boyce, W. T. (2008). Biological sensitivity to context. *Current Directions in Psychological Science, 17*(3), 183-187.
Ellis, B. J., Boyce, W. T., Belsky, J., Bakermans-Kranenburg, M. J., & van Ijzendoorn, M. H. (2011). Differential susceptibility to the environment: an evolutionary--neurodevelopmental theory. *Development Psychopathology, 23*(1), 7-28.
Ellis, B. J., Essex, M. J., & Boyce, W. T. (2005). Biological sensitivity to context: II. Empirical explorations of an evolutionary-developmental theory. *Development and Psychopathology, 17*(2), 303-328.
Ellis, B. J., Shirtcliff, E. A., Boyce, W. T., Deardorff, J., & Essex, M. J. (2011). Quality of early family relationships and the timing and tempo of puberty: effects depend on biological sensitivity to context. *Development Psychopathology, 23*(1), 85-99.
English, D. J., Upadhyaya, M. P., Litrownik, A. J., Marshall, J. M., Runyan, D. K., Graham, J. C., & Dubowitz, H. (2005). Maltreatment's wake: the relationship of maltreatment dimensions to child outcomes. *Child Abuse and Neglect, 29*(15970327), 597-619.
Enns, M. W., Cox, B. J., & Clara, I. (2002). Parental bonding and adult psychopathology: results from the US National Comorbidity Survey. *Psychological Medicine, 32*(6), 997-1008.
Enoch, M. A., Steer, C. D., Newman, T. K., Gibson, N., & Goldman, D. (2010). Early life stress, MAOA, and gene-environment interactions predict behavioral disinhibition in children. *Genes, Brain, and Behavior, 9*(1), 65-74.
Enos, W. F., Jr., Beyer, J. C., & Holmes, R. H. (1955). Pathogenesis of coronary disease in American soldiers killed in Korea. *JAMA - Journal of the American Medical Association, 158*(11), 912-914.
Entringer, S., Buss, C., Kumsta, R., Hellhammer, D., Wadhwa, P., & Wüst, S. (2009). Prenatal psychosocial stress exposure is associated with subsequent working memory performance in young women. *Behavioral Neuroscience, 123*(4), 886-893.
Eriksson, J. G., Forsen, T., Tuomilehto, J., Osmond, C., & Barker, D. J. (2001). Early growth and coronary heart disease in later life: longitudinal study. *British Medical Journal (Clinical Research Edition), 322*(7292), 949-953.
Evans, G. W. (2004). The environment of childhood poverty. *American Psychologist, 59*(2), 77-92.

Evans, G. W., Gonnella, C., Marcynyszyn, L. A., Gentile, L., & Salpekar, N. (2005). The role of chaos in poverty and children's socioemotional adjustment. *Psychological Science, 16*(7), 560-565.
Evans, G. W., & Kim, P. (2007). Childhood poverty and health: cumulative risk exposure and stress dysregulation. *Psychological Science, 18*(11), 953-957.
Evans, G. W., & Schamberg, M. A. (2009). Childhood poverty, chronic stress, and adult working memory. *Proceedings of the National Academy of Sciences of the United States of America*.
Evans, R. G., Barer, M. L., & Marmor, T. R. (1994). *Why are some people healthy and others not? The determinants of health of populations*. New York, NY: Aldine DeGruyter.
Evensen, K. A., Steinshamn, S., Tjonna, A. E., Stolen, T., Hoydal, M. A., Wisloff, U., . . . Vik, T. (2009). Effects of preterm birth and fetal growth retardation on cardiovascular risk factors in young adulthood. *Early Human Development, 85*(4), 239-245.
Fabricius-Bjerre, S., Jensen, R. B., Faerch, K., Larsen, T., Molgaard, C., Michaelsen, K. F., . . . Greisen, G. (2011). Impact of birth weight and early infant weight gain on insulin resistance and associated cardiovascular risk factors in adolescence. *PLoS ONE, 6*(6), e20595.
Fahlke, C., Lorenz, J. G., Long, J., Champoux, M., Suomi, S. J., & Higley, J. D. (2000). Rearing experiences and stress-induced plasma cortisol as early risk factors for excessive alcohol consumption in non-human primates *Alcoholism, Clinical and Experimental Research, 24*(5), 644-650.
Fantuzzo, J., Manz, P., Atkins, M., & Meyers, R. (2005). Peer-mediated treatment of socially withdrawn maltreated preschool children: cultivating natural community resources. *Journal of Child Psychology and Psychiatry and Allied Disciplines, 34*(15901232), 320-325.
Fantuzzo, J., Sutton-Smith, B., Atkins, M., Meyers, R., Stevenson, H., Coolahan, K., . . . Manz, P. (1996). Community-based resilient peer treatment of withdrawn maltreated preschool children. *Journal of Consulting and Clinical Psychology, 64*(8991324), 1377-1386.
Farah, M. J., Shera, D. M., Savage, J. H., Betancourt, L., Giannetta, J. M., Brodsky, N. L., . . . Hurt, H. (2006). Childhood poverty: specific associations with neurocognitive development. *Brain Research, 1110*(1), 166-174.
Feder, A., Nestler, E. J., & Charney, D. S. (2009). Psychobiology and molecular genetics of resilience. *Nature Reviews Neuroscience, 10*(6), 446-457.
Feldman, R., & Eidelman, A. I. (2007). Maternal postpartum behavior and the emergence of infant-mother and infant-father synchrony in preterm and full-term infants: the role of neonatal vagal tone. *Developmental Psychobiology, 49*(3), 290-302.
Feldman, R., Gordon, I., Schneiderman, I., Weisman, O., & Zagoory-Sharon, O. (2010). Natural variations in maternal and paternal care are associated with systematic changes in oxytocin following parent-infant contacts. *Psychoneuroendocrinology, 35*(8), 1133-1141.
Feldman, R., Gordon, I., & Zagoory-Sharon, O. (2010). The cross-generation transmission of oxytocin in humans. *Hormones and Behavior, 58*(4), 669-676.
Feldman, R., Granat, A., Pariente, C., & Kanety, H. (2009). Maternal depression and anxiety across the postpartum year and infant social engagement, fear regulation, and stress reactivity. *Journal of the American Academy of Child and Adolescent Psychiatry, 48*(9), 919.
Felitti, V. J., Anda, R. F., Nordenberg, D., Williamson, D. F., Spitz, A. M., Edwards, V., . . . Marks, J. S. (1998). Relationship of childhood abuse and household dysfunction to many of the leading causes of death in adults - The adverse childhood experiences (ACE) study. *American Journal of Preventive Medicine, 14*(4), 245-258.
Fergusson, D. M., Grant, H., Horwood, L. J., & Ridder, E. M. (2005a). Randomized trial of the Early Start program of home visitation. *Pediatrics, 116*(16322138), 803-809.
Fergusson, D. M., Horwood, L. J., Grant, H., & Ridder, E. (2005b). Early Start evaluation report. Christchurch, New Zealand: Early Start Project Ltd.
Fergusson, D. M., & Lynskey, M. T. (1997). Physical punishment/maltreatment during childhood and adjustment in young adulthood. *Child Abuse and Neglect, 21*(7), 617-630.
Field, T. (1990). Alleviating stress in newborn infants in the intensive care unit. *Clinics in Perinatology, 17*(1), 1-9.
Field, T., Diego, M., & Hernandez-Reif, M. (2009). Depressed mothers' infants are less responsive to faces and voices. *Infant Behavior and Development, 32*(3), 239-244.
Field, T., Hernandez-Reif, M., Diego, M., Feijo, L., Vera, Y., Gil, K., & Sanders, C. (2007). Still-face and separation effects on depressed mother-infant interactions. *Infant Mental Health Journal, 28*(3), 314-323.
Field, T. M., & Goodman, S. H. (2002). Prenatal effects of maternal depression. Children of depressed parents: mechanisms of risk and implications for treatment. In I. H. Gotlib (Ed.), *Children of depressed parents:*

Mechanisms of risk and implications for treatment (pp. 59-88). Washington, DC: American Psychological Association.
Figueira, P., Fernandes Malloy-Diniz, L., Aurélio Romano-Silva, M., Silva Neves, F., & Corrêa, H. (2009). Postpartum depression and comorbid disorders: Frequency and relevance to clinical management. *Archives of Women's Mental Health, 12*(6), 451.
Finkelhor, D., Ormrod, R., Turner, H., & Hamby, S. L. (2005). The victimization of children and youth: a comprehensive, national survey. *Child Maltreatment, 10*(1), 5-25.
Fishbein, D., Warner, T., Krebs, C., Trevarthen, N., Flannery, B., & Hammond, J. (2009). Differential relationships between personal and community stressors and children's neurocognitive functioning. *Child Maltreatment, 14*(4), 299-315.
Fisher, P. A., Gunnar, M. R., Dozier, M., Bruce, J., & Pears, K. C. (2006). Effects of therapeutic interventions for foster children on behavioral problems, caregiver attachment, and stress regulatory neural systems. *Annals of the New York Academy of Sciences, 1094*(17347353), 215-225.
Fitzpatrick, M. J., Ben-Shahar, Y., Smid, H. M., Vet, L. E., Robinson, G. E., & Sokolowski, M. B. (2005). Candidate genes for behavioural ecology. *Trends in Ecology & Evolution, 20*(2), 96-104.
Fleming, A. S., Corter, C., Stallings, J., Steiner, M. (2002). Testosterone and prolactin are associated with emotional responses to infant cries in new fathers. *Hormones and Behavior, 42*(4), 399-413.
Fleming, A. S., Kraemer, G. W., Gonzalez, A., Lovic, V., Rees, S., & Melo, A. (2002). Mothering begets mothering: the transmission of behavior and its neurobiology across generations. *Pharmacology, Biochemistry and Behavior, 73*, 61-75.
Fleming, A. S., & Li, M. (2002). Psychobiology of maternal behavior and its early determinants in nonhuman mammals. In M. H. Bornstein (Ed.), *Handbook of parenting: biology and ecology of parenting* (Vol. 2, pp. 61-97). Mahwah, NJ: Lawrence Erlbaum Associates.
Fleming, A. S., Ruble, D. N., Flett, G. L., & Shaul, D. (1988). Postpartum adjustment in first-time mothers: Relations between mood, maternal attitudes and mother-infant interactions. *Developmental Psychology, 24*, 71-81.
Fleming, A. S., Steiner, M., & Corter, C. (1997). Cortisol, hedonics, and maternal responsiveness in human mothers. *Hormones and Behavior, 32*(2), 85-98.
Fluke, J. D., Shusterman, G. R., Hollinshead, D., & Yuan, Y. T. (2005). Rereporting and recurrence of child maltreatment: findings from NCANDS. Washington, DC: Department of Health and Human Services, Office of the Assistant Secretary for Planning and Evaluation.
Fontaine, N., Carbonneau, R., Barker, E. D., Vitaro, F., Hébert, M., Côté, S. M., . . . Tremblay, R. E. (2008). Girls' hyperactivity and physical aggression during childhood and adjustment problems in early adulthood: a 15-year longitudinal study. *Archives of General Psychiatry, 65*(3), 320-328.
Forget-Dubois, N., Boivin, M., Dionne, G., Pierce, T., Tremblay, R. E., & Pérusse, D. (2007). A longitudinal twin study of the genetic and environmental etiology of maternal hostile-reactive behavior during infancy and toddlerhood. *Infant Behavior and Development, 30*(3), 453-465.
Forget-Dubois, N., Dionne, G., Lemelin, J.-P., Pérusse, D., Tremblay, R. E., & Boivin, M. (2009). Early child language mediates the relation between home environment and school readiness. *Child Development, 80*(3), 736-749.
Forum for Early Child Development Monitoring. Components of a monitoring system. Retrieved August 10, 2012, from http://www.childdevelopmentmonitoring.net/what-we-do
Fossati, P., Ergis, A. M., & Allilaire, J. F. (2001). Problem-solving abilities in unipolar depressed patients: comparison of performance on the modified version of the Wisconsin and the California sorting tests. *Psychiatry Research, 104*(2), 145-156.
Foxcroft, D. R., Ireland, D., Lister-Sharp, D. J., Lowe, G., & Breen, R. (2003). Longer-term primary prevention for alcohol misuse in young people: a systematic review. *Addiction, 98*(4), 397-411.
Francis, D., Diorio, J., Liu, D., & Meaney, M. J. (1999). Nongenomic transmission across generations of maternal behaviour and stress responses in the rat. *Science, 286*, 1155-1158.
Francis, D. D., & Meaney, M. J. (1999). Maternal care and the development of stress responses. *Current Opinion in Neurobiology, 9*(1), 128-134.
Friedman, S. H., & Resnick, P. J. (2008). Postpartum depression: an update. *Women's Health, 5*(3), 287-295.
Furstenberg, F. F., Brooks-Gunn, J., & Morgan, S. P. (1987). Adolescent mothers and their children in later life. *Family Planning Perspectives, 19*(4), 142-151.
Gale, S., & Harlow, B. L. (2003). Postpartum mood disorders: a review of clinical and epidemiological factors. *Journal of Psychosomatic Obstetrics and Gynaecology, 24*(4), 257-266.

Gambone, M. A., Klem, A. M., & Connell, J. P. (2002). Finding out what matters for youth: Testing key links in a community action framework for youth development. Philadelphia, PA: Youth Development Strategies, Inc., and Institute for Research and Reform in Education.

Gara, M. A., Rosenberg, S., & Herzog, E. P. (1996). The abused child as parent. *Child Abuse and Neglect, 20*(9), 797-807.

Gardner, F., Burton, J., & Klimes, I. (2006). Randomised controlled trial of a parenting intervention in the voluntary sector for reducing child conduct problems: outcomes and mechanisms of change. *Journal of Child Psychology and Psychiatry and Allied Disciplines, 47*(11), 1123-1132.

Garfield, R. L., Zuvekas, S. H., Lave, J. R., & Donohue, J. M. (2011). The impact of national health care reform on adults with severe mental disorders. *American Journal of Psychiatry, 168*(5), 486-494.

Garner, B., Wood, S. J., Pantelis, C., & van den Buuse, M. (2007). Early maternal deprivation reduces prepulse inhibition and impairs spatial learning ability in adulthood: no further effect of post-pubertal chronic corticosterone treatment. *Behavioural Brain Research, 176*(2), 323-332.

Gavin, N. I., Gaynes, B. N., Lohr, K. N., Meltzer-Brody, S., Gartlehner, G., & Swinson, T. (2005). Perinatal depression: a systematic review of prevalence and incidence. *Obstetrics and Gynecology, 106*(5), 1071-1083.

Geeraert, L., Van den Noortgate, W., Grietens, H., & al., e. (2004). The effects of early prevention programs for families with young children at risk for physical child abuse and neglect: a meta-analysis. *Child Maltreatment, 9*, 277- 291.

Geoffroy, M.-C., Côté, S. M., Giguère, C.-É., Dionne, G., Zelazo, P. D., Tremblay, R. E., . . . Séguin, J. R. (2010). Closing the gap in academic readiness and achievement: the role of early childcare. *Journal of Child Psychology and Psychiatry and Allied Disciplines, 51*(12), 1359-1367.

Gershater-Molko, R. M., Lutzker, J. R., & Sherman, J. A. (2002). Intervention in child neglect: an applied behavioral perspective. *Aggression and Violent Behavior, 7*(2), 103-124.

Gershater-Molko, R. M., Lutzker, J. R., & Wesch, D. (2003). Project SafeCare: Improving health, safety, and parenting skills in families reported for, and at-risk for child maltreatment. *Journal of Family Violence, 18*(6), 377-386.

Gianaros, P. J., Horenstein, J. A., Cohen, S., Matthews, K. A., Brown, S. M., Flory, J. D., . . . Hariri, A. R. (2007). Perigenual anterior cingulate morphology covaries with perceived social standing. *Social Cognitive and Affective Neuroscience, 2*(3), 161-173.

Giardino, J., Gonzalez, A., Steiner, M., & Fleming, A. S. (2008). Effects of motherhood on physiological and subjective responses to infant cries in teenage mothers: a comparison with non-mothers and adult mothers. *Hormones and Behavior, 53*(1), 149-158.

Gibson, G., & Muse, S. (2009). *A primer of genome science* (Third Edition ed.). Sunderland, MA: Sinauer Associates, Inc.

Gilman, S. E., Kawachi, I., Fitzmaurice, G. M., & Buka, L. (2003). Socio-economic status, family disruption and residential stability in childhood: relation to onset, recurrence and remission of major depression. *Psychological Medicine, 33*(8), 1341-1355.

Glaser, D. (2002). Emotional abuse and neglect (psychological maltreatment): a conceptual framework. *Child Abuse and Neglect, 26*(12201163), 697-714.

Glaser, D. P., Prior, V., & Lynch, M. A. (2001). Emotional abuse and emotional neglect: antecedents, operational definitions and consequences. York, UK: British Association for the Study and Prevention of Child Abuse and Neglect (BASPCAN).

Glover, V., O'Connor, T. G., & O'Donnell, K. (2010). Prenatal stress and the programming of the HPA axis. *Neuroscience and Biobehavioral Reviews, 35*(1), 17-22.

Gluckman, P. D., & Hanson, M. A. (2004). The developmental origins of the metabolic syndrome. *Trends in Endocrinology and Metabolism, 15*(4), 183-187.

Gluckman, P. D., Hanson, M. A., & Beedle, A. S. (2007). Early life events and their consequences for later disease: a life history and evolutionary perspective. *American Journal of Human Biology, 19*(1), 1-19.

Gold, P. W., & Chrousos, G. P. (2002). Organization of the stress system and its dysregulation in melancholic and atypical depression: high vs low CRH/NE states. *Molecular Psychiatry, 7*(3), 254-275.

Goldman, D., Oroszi, G., & Ducci, F. (2005). The genetics of addictions: uncovering the genes. *Nature Reviews. Genetics, 6*(7), 521-532.

Gomby, D. S. (2000). Promise and limitations of home visitation. *JAMA: Journal of the American Medical Association, 284*(11), 1430-1431.

Gonzalez, A., Jenkins, J., Steiner, M., & Fleming, A. S. (2012). Maternal early life experiences and parenting: the mediating role of cortisol and executive function. *Journal of the American Academy of Child and Adolescent Psychiatry, 51*(7), 673-682.

Gonzalez, A., Lovic, V., Ward, G. R., Wainwright, P. E., & Fleming, A. S. (2001). Intergenerational effects of complete maternal deprivation and replacement stimulation on maternal bheavor and emotionality in female rats. *Developmental Psychobiology, 38*, 11-32.

Goodman, J. H. (2004). Paternal postpartum depression, its relationship to maternal postpartum depression, and implications for family health. *Journal of Advanced Nursing, 45*(1), 26-35.

Goodman, S. H., & Gotlib, I. H. (Eds.). (2002). *Children of depressed parents: alternative pathways to risk for psychopathology*. Washington, DC: American Psychological Association Press.

Goodwin, D. W., Schulsinger, F., Hermansen, L., Guze, S. B., & Winokur, G. (1973). Alcohol problems in adoptees raised apart from alcoholic biological parents. *Archives of General Psychiatry, 28*(2), 238-243.

Gordon, I., Zagoory-Sharon, O., Leckman, J. F., & Feldman, R. (2010a). Oxytocin and the development of parenting in humans. *Biological Psychiatry, 68*(4), 377-382.

Gordon, I., Zagoory-Sharon, O., Leckman, J. F., & Feldman, R. (2010b). Prolactin, oxytocin, and the development of paternal behavior across the first six months of fatherhood. *Hormones and Behavior, 58*(3), 513-518.

Goyal, D., Gay, C., & Lee, K. (2009). Fragmental maternal sleep is more strongly correlated with depressive symptoms than infant temperament at three months postpartum. *Archives of Women's Mental Health, 12*(4), 229-237.

Graham-Bermann, S. A., Lynch, S., Banyard, V., DeVoe, E. R., & Halabu, H. (2007). Community-based intervention for children exposed to intimate partner violence: an efficacy trial. *Journal of Consulting and Clinical Psychology, 75*(17469878), 199-209.

Grantham-McGregor, S., Walker, S., Chang, S., & Powell, C. (1997). Effects of early childhood supplementation with and without stimulation on later development in stunted Jamaican children. *American Journal of Clinical Nutrition, 66*(2), 247-253.

Gray, J. D., Cutler, C. A., Dean, J. G., & Kempe, C. H. (1979). Prediction and prevention of child abuse and neglect. *Journal of Social Issues, 35*(2), 127-139.

GRIP Research Unit on Children's Psychosocial Maladjustment. Longitudinal and Experimental Study of low SES boys in Montréal (ÉLEM). Retrieved August 30, 2012, from http://www.gripinfo.ca/grip/consultation/etudes/infogen.asp?langue=en&ts=1149085054203&id_etude=1

Groer, M. W. (2005). Differences between exclusive breastfeeders, formula-feeders, and controls: a study of stress, mood, and endocrine variables. *Biological Research for Nursing, 7*(2), 106-117.

Groer, M. W., & Moran, K. (2007). Immune, health and endocrine characteristics of depressed postpartum mothers. *Psychoneuroendocrinology, 32*(2), 133-139.

Gump, B. B., Reihman, J., Stewart, P., Lonky, E., Darvill, T., & Matthews, K. A. (2007). Blood lead (Pb) levels: a potential environmental mechanism explaining the relation between socioeconomic status and cardiovascular reactivity in children. *Health Psychology, 26*(3), 296-304.

Gump, B. B., Reihman, J., Stewart, P., Lonky, E., Darvilla, T., Grangera, D. A., & Matthewsa, K. A. (2009). Trajectories of maternal depressive symptoms over her child's life span: Relation to adrenocortical, cardiovascular, and emotional functioning in children. *Development and Psychopathology, 21*(1), 207-225.

Gunnar, M. R., Brodersen, L., Nachmias, M., Buss, K., & Rigatuso, J. (1996). Stress reactivity and attachment security. *Developmental Psychobiology, 29*(3), 191-204.

Gunnar, M. R., & Fisher, P. A. (2006). Early Experience, Stress, and Prevention Network. Bringing basic research on early experience and stress neurobiology to bear on preventative interventions for neglected and maltreated children. *Developmental Psychopathology, 18*(3), 651-677.

Gunnar, M. R., Morison, S. J., Chisholm, K., & Schuder, M. (2001). Salivary cortisol levels in children adopted from Romanian orphanages. *Development and Psychopathology, 13*, 611-628.

Gunnar, M. R., Wewerka, S., Frenn, K., Long, J. D., & Griggs, C. (2009). Developmental changes in hypothalamus-pituitary-adrenal activity over the transition to adolescence: normative changes and associations with puberty. *Developmental Psychopathology, 21*(1), 69-85.

Gutteling, B. M., de Weerth, C., & Buitelaar, J. K. (2005). Prenatal stress and children's cortisol reaction to the first day of school. *Psychoneuroendocrinology, 30*(6), 541-549.

Haapasalo, J., & Tremblay, R. E. (1994). Physically aggressive boys from ages 6 to 12: family background, parenting behavior, and prediction of delinquency. *Journal of Consulting and Clinical Psychology, 62*(5), 1044-1052.

Haber, J. R., Jacob, T., & Heath, A. C. (2005). Paternal alcoholism and offspring conduct disorder: evidence for the 'common genes' hypothesis. *Twin Research and Human Genetics, 8*(15901475), 120-131.
Hackman, D. A., & Farah, M. J. (2009). Socioeconomic status and the developing brain. *Trends in Cognitive Sciences, 13*(2), 65-73.
Hackman, D. A., Farah, M. J., & Meaney, M. J. (2010). Socioeconomic status and the brain: mechanistic insights from human and animal research. *Nature Reviews Neuroscience, 11*(9), 651-659.
Halligan, S. L., Murray, L., Martins, C., & Cooper, P. J. (2007). Maternal depression and psychiatric outcomes in adolescent offspring: a 13-year longitudinal study. *Journal of Affective Disorders, 97*(1-3), 145-154.
Hammen, C., Henry, R., & Daley, S. E. (2000). Depression and sensitization to stressors among young women as a function of childhood adversity. *Journal of Consulting and Clinical Psychology, 68*(5), 782-787.
Hanson, J. L., Chung, M. K., Avants, B. B., Shirtcliff, E. A., Gee, J. C., Davidson, R. J., & Pollak, S. D. (2010). Early stress Is associated with alterations in the orbitofrontal cortex: a tensor-based morphometry investigation of brain structure and behavioral risk *Journal of Neuroscience, 3*-(22), 7466-7472.
Hardt, J., & Rutter, M. (2004). Validity of adult retrospective reports of adverse childhood experiences: review of the evidence. *Journal of Child Psychology and Psychiatry and Allied Disciplines, 45*(2), 260-273.
Hardy, J. B., & Streett, R. (1989). Family support and parenting education in the home: an effective extension of clinic-based preventive health care services for poor children. *Journal of Pediatrics, 115*(6), 927-931.
Harkness, K. L., & Monroe, S. M. (2002). Childhood adversity and the endogenous versus nonendogenous distinction in women with major depression. *American Journal of Psychiatry, 159*(3), 387-393.
Hart, T., & Risley, T. R. (1995). *Meaningful differences in the everyday experience of young American children*. Baltimore, MD: Paul H.Brookes.
Hartley, C. A., Fischl, B., & Phelps, E. A. (2011). Brain structure correlates of individual differences in the acquisition and inhibition of conditioned fear. *Cerebral Cortex*.
Harvey, E., Danforth, J. S., McKee, T. E., Ulaszek, W. R., & Friedman, J. L. (2003). Parenting of children with attention-defecit/hyperactivity disorder (ADHD): the role of parental ADHD symptomatology. *Journal of Attention Disorders, 7*(1), 31-42.
Hatch, E. E., Palmer, J. R., Titus-Ernstoff, L., Noller, K. L., Kaufman, R. H., Mittendorf, R., . . . Hoover, R. N. (1998). Cancer risk in women exposed to diethylstilbestrol in utero. *JAMA: Journal of the American Medical Association, 280*(7), 630-634.
Hazel, N. A., Hammen, C., Brennan, P. A., & Najman, J. (2008). Early childhood adversity and adolescent depression: the mediating role of continued stress. *Psychological Medicine, 38*(4), 581-589.
Health Canada. (2010). Canadian Alcohol and Drug Use Monitoring Survey. Summary of results for 2010. from http://www.hc-sc.gc.ca/hc-ps/drugs-drogues/stat/_2010/summary-sommaire-eng.php#intro
Heckman, J. J. (2006). Skill formation and the economics of investing in disadvantaged children. *Science, 312*(5782), 1900-1902.
Heils, A., Teufel, A., Petri, S., Stober, G., Riederer, P., Bengel, D., & Lesch, K. P. (1996). Allelic variation of human serotonin transporter gene expression. *Journal of Neurochemistry, 66*(6), 2621-2624.
Heim, C., Ehlert, U., & Hellhammer, D. H. (2000). The potential role of hypocortisolism in the pathophysiology of stress-related bodily disorders. *Psychoneuroendocrinology, 25*(1), 1-35.
Heim, C., & Nemeroff, C. B. (1999). The impact of early adverse experiences on brain systems involved in the pathophysiology of anxiety and affective disorders. *Biological Psychiatry, 46*(11), 1509-1522.
Heim, C., Newport, D. J., Mletzko, T., Miller, A. H., & Nemeroff, C. B. (2008). The link between childhood trauma and depression: insights from HPA axis studies in humans. *Psychoneuroendocrinology, 33*(6), 693-710.
Heim, C., Plotsky, P. M., & Nemeroff, C. B. (2004). Importance of studying the contributions of early adverse experience to neurobiological findings in depression. *Neuropsychopharmacology, 29*(4), 641-648.
Hensch, T. K. (2005). Critical period plasticity in local cortical circuits. *Nature Reviews Neuroscience, 6*(11), 877-888.
Herrera, E., Reissland, N., & Shepherd, J. (2004). Maternal touch and maternal child-directed speech: effects of depressed mood in the postnatal period. *Journal of Affective Disorders, 81*(1), 29-39.
Hertzman, C., & Boyce, T. (2010). How experience gets under the skin to create gradients in developmental health. *Annual Review of Public Health, 31*, 329-347.
Hertzman, C., & Power, C. (2003). Health and human development: understandings from life-course research. *Developmental Neuropsychology, 24*(2-3), 719-744.
Higley, J. D., Mehlman, P. T., Taub, D. M., Higley, S. B., Suomi, S. J., Vickers, J. H., & M., L. (1992). Cerebrospinal fluid monoamine and adrenal correlates of aggression in free-ranging rhesus monkeys. *Archives of General Psychiatry, 49*(6), 436-441.

Higley, J. D., Suomi, S. J., & Linnoila, M. (1991). CSF monoamine metabolite concentrations vary according to age, rearing, and sex, and are influenced by the stressor of social separation in rhesus monkeys. *Psychopharmacology, 103*(4), 551-556.

Hillis, S. D., Anda, R. F., Dube, S. R., Felitti, V. J., Marchbanks, P. A., & Marks, J. S. (2004). The association between adverse childhood experiences and adolescent pregnancy, long-term psychosocial consequences, and fetal death. *Pediatrics, 113*(2), 320-327.

Holmes, A., & Wellman, C. L. (2009). Stress-induced prefrontal reorganization and executive dysfunction in rodents. *Neuroscience and Biobehavioral Reviews, 33*(6), 773-783.

Hopfer, C. J., Crowley, T. J., & Hewitt, J. K. (2003). Review of twin and adoption studies of adolescent substance use. *Journal of the American Academy of Child and Adolescent Psychiatry, 42*(6), 710-719.

Houweling, T. A., Caspar, A. E., Looman, W. N., & Mackenbach, J. P. (2005). Determinants of under-5 mortality among the poor and the rich: a cross-national analysis of 43 developing countries. *International Journal of Epidemiology, 34*(6), 1257-1265.

Houweling, T. A., & Kunst, A. E. (2009). Socio-economic inequalities in childhood mortality in low- and middle-income countries: a review of the international evidence. *British Medical Journal (Clinical Research Edition), 93*, 7-26.

Hrdy, J., Zanvit, P., Novotna, O., Kocourkova, I., Zizka, J., & Prokesova, L. (2010). Cytokine expression in cord blood cells of children of healthy and allergic mothers. *Folia Microbiologica, 55*(5), 515-519.

Hughes, J. R., & Gottlieb, L. N. (2004). The effects of the Webster-Stratton parenting program on maltreating families: fostering strengths. *Child Abuse and Neglect, 28*(15519437), 1081-1097.

Huijbregts, S. J., Séguin, J. R., Zoccolillo, M., Boivin, M., & Tremblay, R. E. (2008). Maternal prenatal smoking, parental antisocial behavior, and early childhood physical aggression. *Development and Psychopathology, 20*(2), 437-453.

Hutchings, J., Gardner, F., Bywater, T., Daley, D., Whitaker, C., Jones, K., . . . Edwards, R. T. (2007). Parenting intervention in Sure Start services for children at risk of developing conduct disorder: pragmatic randomised controlled trial. *British Medical Journal (Clinical Research Edition), 334*(7595), 678.

Huxley, P., & Warner, R. (1993). Primary prevention of parenting dysfunction in high-risk cases. *American Journal of Orthopsychiatry, 63*(8267098), 582-588.

Iacono, W. G., Malone, S. M., & McGue, M. (2008). Behavioral disinhibition and the development of early-onset addiction: common and specific influences. *Annual Review of Clinical Psychology, 4*, 325-348.

Institut de la statistique du Québec. Quebec Longitudinal Study of Child Development in Quebec (QLSCD). Retrieved September 5, 2012, from http://www.iamillbe.stat.gouv.qc.ca/default_an.htm

Irwin, L. G. (2006). The potential contribution of emancipatory research methodologies to the field of child health. *Nursing Inquiry, 13*(2), 94-102.

Irwin, L. G., & Johnson, J. (2005). Interviewing young children: explicating our practices and dilemmas. *Qualitative Health Research, 15*(6), 821-831.

Jaffee, S. R., Caspi, A., Moffitt, T. E., Dodge, K. A., Rutter, M., Taylor, A., & Tully, L. A. (2005). Nature X nurture: Genetic vulnerabilities interact with physical maltreatment to promote conduct problems. *Developmental Psychopathology, 17*(15971760), 67-84.

Jaffee, S. R., Caspi, A., Moffitt, T. E., Polo-Tomas, M., Price, T. S., & Taylor, A. (2004a). The limits of child effects: evidence for genetically mediated child effects on corporal punishment but not on physical maltreatment. *Developmental Psychology, 40*(15535755), 1047-1058.

Jaffee, S. R., Caspi, A., Moffitt, T. E., Polo-Tomas, M., & Taylor, A. (2007). Individual, family, and neighborhood factors distinguish resilient from non-resilient maltreated children: a cumulative stressors model. *Child Abuse and Neglect, 31*(3), 231-253.

Jaffee, S. R., Caspi, A., Moffitt, T. E., & Taylor, A. (2004b). Physical maltreatment victim to antisocial child: evidence of an environmentally mediated process. *Journal of Abnormal Psychology, 113*(14992656), 44-55.

Jaffee, S. R., & Price, T. S. (2007). Gene-environment correlations: a review of the evidence and implications for prevention of mental illness. *Molecular Psychiatry, 12*(5), 432-442.

James, A. (1993). *Childhood identities: self and social relationships in the experience of the child*. Edinburgh: Edinburgh University Press.

Jenkins-Smith, H. C., & Sabatier, P. A. (1994). Evaluating the advocacy coalition framework. *Journal of Public Policy, 14*(2), 175-203.

Jenkins, J., Rasbash, J., Leckie, G., Gass, K., & Dunn, J. (2012). The role of maternal factors in sibling relationship quality: a multilevel study of multiple dyads per family. *Journal of Child Psychology and Psychiatry and Allied Disciplines, 53*(6), 622-629.

Jirtle, R. L., & Skinner, M. K. (2007). Environmental epigenomics and disease susceptibility. *Nature Reviews Genetics, 8*(4), 253-262.
Jolley, S. N., Elmore, S., Barnard, K. E., & Carr, D. B. (2007). Dysregulation of the hypothalamic-pituitary-adrenal axis in postpartum depression. *Biological Research for Nursing, 8*(3), 210-222.
Joly, M.P., Boivin, M., Junker, A., Bocking, A., Kramer, M., Atkinson, S.A., (2012). An Inventory of Canadian Pregnancy and Birth Cohort Studies: Research in Progress. *BMC Pregnancy and Childbirth,* 12:117.
Jonson-Reid, M., & Barth, R. P. (2000). From placement to prison: The path to adolescent incarceration from child welfare supervised foster or group care. *Children and Youth Services Review, 22*(7), 493-516.
Jonson-Reid, M., & Barth, R. P. (2003). Probation foster care as an outcome for children exiting child welfare foster care. *Social Work, 48*(3), 348-361.
Jouriles, E. N., McDonald, R., Rosenfield, D., Stephens, N., Corbitt-Shindler, D., & Miller, P. C. (2009). Reducing conduct problems among children exposed to intimate partner violence: a randomized clinical trial examining effects of Project Support. *Journal of Consulting and Clinical Psychology, 77*(4), 705-717.
Jouriles, E. N., McDonald, R., Spiller, L., Norwood, W. D., Swank, P. R., Stephens, N., . . . Buzy, W. M. (2001). Reducing conduct problems among children of battered women. *Journal of Consulting and Clinical Psychology, 69*(5), 774-785.
Kamerman, S. B., & Kahn, A. J. (1993). Home health visiting in Europe. *Future of Children, 3*(3), 39-52.
Kamerman, S. B., Neuman, M., Waldfogel, J., & Brooks-Gunn, J. (2003). *Social policies, family types, and child outcomes in selected OECD countries*. OECD Social, Employment, and Migration Working Papers 6. OECD. Paris, France.
Kammerer, M., Taylor, A., & Glover, V. (2006). The HPA axis and perinatal depression: a hypothesis. *Archives of Women's Mental Health, 9*(4), 187-196.
Kane, P., & Garber, J. (2004). The relations among depression in fathers, children's psychopathology, and father-child conflict: a meta-analysis. *Clinical Psychology Review, 24*(3), 339-360.
Kaplow, J. B., & Widom, C. S. (2007). Age of onset of child maltreatment predicts long-term mental health outcomes. *Journal of Abnormal Psychology, 116*(17324028), 176-187.
Kapoor, A., Dunn, E., Kostaki, A., Andrews, M. H., & Matthews, S. G. (2006). Fetal programming of hypothalamo-pituitary-adrenal function: prenatal stress and glucocorticoids. *Journal of Physiology and Biochemistry, 572*(1), 31-44.
Kapoor, A., & Matthews, S. G. (2005). Short periods of prenatal stress affect growth, behaviour and hypothalamo-pituitary-adrenal axis activty in male guinea pig offspring. *Journal of Physiology, 566*(3), 967-977.
Kapoor, A., & Matthews, S. G. (2008). Prenatal stress modifies behavior and hypothalamic-pituitary-adrenal function in female guinea pig offspring: effects of timing of prenatal stress and stage of reproductive cycle. *Endocrinology, 149*(12), 6406-6415.
Karevold, E., Røysam, E., Ystrom, E., & Mathiesen, K. S. (2009). Predictors and pathyways from infancy to symptoms of anxiety and depression in early adolescence. *Developmental Psychology, 45*(4), 1051-1060.
Karg, K., Burmeister, M., Shedden, K., & Sen, S. (2011). The serotonin transporter promoter variant (5-httlpr), stress, and depression meta-analysis revisited: evidence of genetic moderation. *Archives of General Psychiatry, 68*(5), 444-454.
Karlamangla, A. S., Singer, B. H., McEwen, B. S., Rowe, J. W., & Seeman, T. E. (2002). Allostatic load as a predictor of functional decline.MacArthur studies of successful aging. *Journal of Clinical Epidemiology, 55*(7), 696-710.
Kaufman, J., Yang, B., Douglas-Palumberi, H., Houshyar, S., Lipschitz, D., Krystal, J. H., & Gelernter, J. (2004). Social supports and serotonin transporter gene moderate depression in maltreated children. *Proceedings of the National Academy of Sciences of the United States of America, 101*(49), 17316-17321.
Kauppi, A., Kumpulainen, K., Vanamo, T., Merikanto, J., & Karkola, K. (2008). Maternal depression and filicide-case study of ten mothers *Archives of Women's Mental Health, 11*(3), 201-206.
Kawachi, I., Adler, N. E., & Dow, W. H. (2010). Money, schooling, and health: mechanisms and causal evidence. *Annals of the New York Academy of Sciences, 1186*, 56-68.
Keating, D. P., & Hertzman, C. (Eds.). (1999). *Developmental health and the wealth of nations: social, biological, and educational dynamics*. New York, NY: Guilford Press.
Keenan, H. T., & Leventhal, J. M. (2010). A case-control study to evaluate Utah's shaken baby prevention program. *Academic Pediatrics, 10*(21075319), 389-394.
Keller, H., Borke, J., Yovsi, R., Lohaus, A., & Jensen, H. (2005). Cultural orientations and historical changes as predictors of parenting behaviour. *International Journal of Behavioral Development, 29*(3), 229-237.

Keller, H., Yovsi, R., Borke, J., Kartner, J., Jensen, H., & Papaligoura, Z. (2004). Developmental consequences of early parenting experiences: self-recognition and self-regulation in three cultural communities. *Child Development, 75*(6), 1745-1760.

Kendler, K. S., & Baker, J. H. (2007). Genetic influences on measures of the environment: a systematic review. *Psychological Medicine, 37*(5), 615-626.

Kent, C. F., Daskalchuk, T., Cook, L., Sokolowski, M. B., & Greenspan, R. J. (2009). The Drosophila foraging gene mediates adult plasticity and gene-environment interactions in behaviour, metabolites, and gene expression in response to food deprivation. *PLoS Genet, 5*(8), e1000609.

Kentner, A. C., Abizaid, A., & Bielajew, C. (2010). Modeling dad: animal models of paternal behavior. *Neuroscience and Biobehavioral Reviews, 34*(3), 438-451.

Kershaw, P., & Anderson, L. (2011). Does Canada work for all generations? National summary. Vancouver, BC: University of British Columbia, Human Early Learning Partnership.

Kessler, R. C., Pecora, P. J., Williams, J., Hiripi, E., O'Brien, K., English, D., . . . Sampson, N. A. (2008). Effects of enhanced foster care on the long-term physical and mental health of foster care alumni. *Archives of General Psychiatry, 65*(18519820), 625-633.

Khan, Y., & Bhutta, Z. A. (2010). Nutritional deficiencies in the developing world: current status and opportunities for intervention. *Pediatric Clinics of North America, 57*(6), 1409-1441.

Kiely, M., El-Mohandes, A. A. E., El-Khorazaty, M. N., & Gantz, M. G. (2010). An integrated intervention to reduce intimate partner violence in pregnancy: a randomized controlled trial. *Obstetrics and Gynecology, 115*(20093899), 273-283.

Kim-Cohen, J., Caspi, A., Moffitt, T. E., Harrington, H., Milne, B. J., & Poulton, R. (2003). Prior juvenile diagnoses in adults with mental disorder - Developmental follow-back of a prospective-longitudinal cohort. *Archives of General Psychiatry, 60*(7), 709-717.

Kim, P., Leckman, J. F., Mayes, L. C., Newman, M.-A., Feldman, R., & Swain, J. E. (2010). Perceived quality of maternal care in childhood and structure and function of mothers' brain. *Developmental Science, 13*(4), 662-673.

Kinnally, E. L., Tarara, E. R., Mason, W. A., Mendoza, S. P., Abel, K., Lyons, L. A., & Capitanio, J. P. (2010). Serotonin transporter expression is predicted by early life stress and is associated with disinhibited behavior in infant rhesus macaques. *Genes, Brain, and Behavior, 9*(1), 45-52.

Kishiyama, M. M., Boyce, W. T., Jimenez, A. M., Perry, L. M., & Knight, R. T. (2009). Socioeconomic disparities affect prefrontal function in children. *Journal of Cognitive Neuroscience, 21*(6), 1106-1115.

Kitzman, H., Olds, D. L., Cole, R. E., Hanks, C. A., Anson, E. A., Arcoleo, K. J., . . . Holmberg, J. R. (2010). Enduring effects of prenatal and infancy home visiting by nurses on children: follow-up of a randomized trial among children at age 12 years. *Archives of Pediatrics and Adolescent Medicine, 164*(5), 412-418.

Kitzman, H., Olds, D. L., Henderson, C. R., Hanks, C., Cole, R., Tatelbaum, R., . . . Barnard, K. (1997). Effect of prenatal and infancy home visitation by nurses on pregnancy outcomes, childhood injuries, and repeat childbearing. A randomized controlled trial. *JAMA: Journal of the American Medical Association, 278*(8), 644-652.

Klaus, M. H., Trause, M. A., & Kennell, J. H. (1975). Does human maternal behaviour after delivery show a characteristic pattern? *Ciba Found Symposium, 33*, 69-85.

Klein, S., & McCarthy, D. (2009). North Carolina's ABCD program: using community care networks to improve the delivery of childhood developmental screening and referral to early intervention services. *Issue brief, 66*, 1-28.

Kling, J. R., Ludwig, J., & Katz, L. F. (2005). Neighborhood effects on crime for female and male youth: evidence from a randomized housing voucher experiment. *Quarterly Journal of Economics, 120*(1), 87-130.

Knudsen, E. I., Heckman, J. J., Cameron, J. L., & Shonkoff, J. P. (2006). Economic, neurobiological, and behavioral perspectives on building America's future workforce. *Proceedings of the National Academy of Sciences of the United States of America, 103*(27), 10155-10162.

Knutson, J. F. (1995). Psychological characteristics of maltreated children: putative risk factors and consequences. *Annual Review of Psychology, 46*, 401-431.

Kochanska, G., Coy, K. C., Tjebkes, T. L., & Husarek, S. J. (1998). Individual differences in emotionality in infancy. *Child Development, 69*(2), 375-390.

Koh, E., & Testa, M. F. (2011). Children discharged from kin and non-kin foster homes: do the risks of foster care re-entry differ? *Children and Youth Services Review, 33*(9), 1497-1505.

Kohen, D. E., Brooks-Gunn, J., Leventhal, T., & Hertzman, C. (2002). Neighborhood income and physical and social disorder in Canada: associations with young children's competencies. *Child Development, 73*(6), 1844-1860.

Kolko, D. J. (1996). Clinical monitoring of treatment course in child physical abuse: psychometric characteristics and treatment comparisons. *Child Abuse and Neglect, 20*(8640423), 23-43.

Koo, V., Lynch, J., & Cooper, S. (2003). Risk of postnatal depression after emergency delivery. *Journal of Obstetrics and Gynaecology Research, 29*(4), 246-250.

Koob, G. F., & Volkow, N. D. (2010). Neurocircuitry of addiction. *Neuropsychopharmacology, 35*(1), 217-238.

Koopmans, J. R., Slutske, W. S., van Baal, G. C., & Boomsma, D. I. (1999). The influence of religion on alcohol use initiation: evidence for genotype X environment interaction. *Behavior Genetics, 29*(6), 445-453.

Kraemer, H. C., Kazdin, A. E., Offord, D. R., Kessler, R. C., Jensen, P. S., & Kupfer, D. J. (1997). Coming to terms with the terms of risk. *Archives of General Psychiatry, 54*(9107150), 337-343.

Kraemer, H. C., Stice, E., Kazdin, A., Offord, D., & Kupfer, D. (2001). How do risk factors work together? Mediators, moderators, and independent, overlapping, and proxy risk factors. *American Journal of Psychiatry, 158*(6), 848-856.

Kramer, M. S. (2000). Invited commentary: association between restricted fetal growth and adult chronic disease: is it causal? Is it important? *American journal of epidemiology, 152*(7), 605-608.

Kratzer, L., & Hodgins, S. (1997). Adult outcomes of child conduct problems: a cohort study. *Journal of Abnormal Child Psychology, 25*(9093901), 65-81.

Kreppner, J. M., O'Connor, T. G., & Rutter, M. (2001). Can inattention/overactivity be an institutional deprivation syndrome? *Journal of Abnormal Child Psychology, 29*(6), 513-528.

Kroenke, C. (2008). Socioeconomic status and health: youth development and neomaterialist and psychosocial mechanisms. *Social Science and Medicine, 66*(1), 31-42.

Kroes, G. (2008). Aboriginal youth in Canada: Emerging issues, research priorities, and policy. Report of the Roundtable on Aboriginal Youth. Setting the medium-term research agenda: Key pressures and emerging issues. Ottawa, ON: Policy Research Initiative, Government of Canada.

Krpan, K. M., Coombs, R., Zinga, D., Steiner, M., & Fleming, A. S. (2005). Experiential and hormonal correlates of maternal behavior in teen and adult mothers. *Hormones and Behavior, 47*(1), 112-122.

Krugman, S. D., Lane, W. G., & Walsh, C. M. (2007). Update on child abuse prevention. *Current Opinion in Pediatrics, 19*(18025942), 711-718.

Kuh, D., & Ben-Shlomo, Y. (Eds.). (2004). *A life course approach to chronic disease epidemiology*. Oxford, UK: Oxford University Press.

Kutcher, S., & McLuckie, A. (2010). Evergreen: A child and youth mental health framework for Canada. Ottawa, ON: Mental Health Commission of Canada.

Lacourse, E., Cŏté, S., Nagin, D. S., Vitaro, F., Brendgen, M., & Tremblay, R. E. (2002). A longitudinal-experimental approach to testing theories of antisocial behavior development. *Development and Psychopathology, 14*(4), 909-924.

Landsverk, J., Carrilio, T., Connelly, C. D., Ganger, W., Slymen, D., Newton, R., & al., e. (2002). Healthy Families San Diego clinical trial: technical report. San Diego, CA: Stuart Foundation, California Wellness Foundation, State of California Department of Social Services: Office of Child Abuse Prevention.

Larson, C. P. (1980). Efficacy of prenatal and postpartum home visits on child health and development. *Pediatrics, 66*(7402804), 191-197.

Lawlor, D. A., Ben-Shlomo, Y., & Leon, D. A. (2004). Pre-adult influences on cardiovascular disease. In D. Kuh & Y. Ben-Shlomo (Eds.), *A life course approach to choronic disease epidemiology* (2nd ed.). Oxford, UK: Oxford University Press.

Lawrence, C. R., Carlson, E. A., & Egeland, B. (2006). The impact of foster care on development. *Development and Psychopathology, 18*(16478552), 57-76.

Lealman, G., Phillips, J., Haigh, D., Stone, J., & Ord-Smith, C. (1983). Prediction and prevention of child abuse? An empty hope? *Lancet, 321*(8339), 1423-1424.

Leblanc, N., Boivin, M., Dionne, G., Brendgen, M., Vitaro, F., Tremblay, R. E., & Pérusse, D. (2008). The development of hyperactive-impulsive behaviors during the preschool years: the predictive validity of parental assessments. *Journal of Abnormal Child Psychology, 36*(7), 977-987.

Lee, C., Barr, R. G., Catherine, N., & Wicks, A. (2007). Age-related incidence of publicly reported shaken baby syndrome cases: is crying a trigger for shaking? *Journal of Developmental and Behavioral Pediatrics, 28*(17700080), 288-293.

Lee, S. S., Chronis-Tuscano, A., Keenan, K., Pelham, W. E., Loney, J., Van Hulle, C. A., . . . Lahey, B. B. (2010). Association of maternal dopamine transporter genotype with negative parenting: evidence for gene x environment interaction with child disruptive behavior. *Molecular Psychiatry, 15*(5), 548-558.

Legrand, L. N., Keyes, M., McGue, M., Iacono, W. G., & Krueger, R. F. (2008). Rural environments reduce the genetic influence on adolescent substance use and rule-breaking behavior. *Psychological Medicine, 38*(9), 1341-1350.

Leibenluft, E., Gobbini, M. I., Harrison, T., & Haxby, J. V. (2004). Mothers' neural activation in response to pictures of their children and other children. *Biological Psychiatry, 56*(4), 225-232.

Lemelin, J.-P., Boivin, M., Forget-Dubois, N., Dionne, G., Séguin, J. R., Brendgen, M., . . . Pérusse, D. (2007). The genetic-environmental etiology of cognitive school readiness and later academic achievement in early childhood. *Child Development, 78*(6), 1855-1869.

Lerner, R. M. (1996). Relative plasticity, integration, temporality, and diversity in human development: a developmental contextual perspective about theory, process, and method. *Developmental Psychology, 32*(4), 781-786.

Leve, L. D., Fisher, P. A., & Chamberlain, P. (2009). Multidimensional treatment foster care as a preventive intervention to promote resiliency among youth in the child welfare system. *Journal of Personality, 77*(19807861), 1869-1902.

Leventhal, J. M., Martin, K. D., & Asnes, A. G. (2010). Fractures and traumatic brain injuries: abuse versus accidents in a US database of hospitalized children. *Pediatrics, 126*(20530077), 104-115.

Leventhal, T., & Brooks-Gunn, J. (2000). The neighborhoods they live in: the effects of neighborhood residence on child and adolescent outcomes. *Psychological Bulletin, 126*(2), 309-337.

Levine, S. (1994). The ontogeny of the hypothalamic-pituitary-adrenal axis. the influence of maternal factors. *Annals of the New York Academy of Sciences, 746*(1), 275-288.

Levitan, R. D., Rector, N. A., Sheldon, T., & Goering, P. (2003). Childhood adversities associated with major depression and/or anxiety disorders in a community sample of Ontario: issues of co-morbidity and specificity. *Depression and Anxiety, 17*(1), 34-42.

Lieberman, A. F., Ghosh Ippen, C., & Van Horn, P. (2006). Child-parent psychotherapy: 6-month follow-up of a randomized controlled trial. *Journal of the American Academy of Child and Adolescent Psychiatry, 45*(16865033), 913-918.

Lieberman, A. F., Van Horn, P., & Ippen, C. G. (2005). Toward evidence-based treatment: Child-parent psychotherapy with preschoolers exposed to marital violence. *Journal of the American Academy of Child and Adolescent Psychiatry, 44*(12), 1241-1248.

Linares, L. O., Montalto, D., Li, M., & Oza, V. S. (2006). A promising parenting intervention in foster care. *Journal of Consulting and Clinical Psychology, 74*(1), 32-41.

Lizardi, H., Klein, D. N., Ouimette, P. C., Riso, L. P., Anderson, R. L., & Donaldson, S. K. (1995). Reports of the childhood home environment in early-onset dysthymia and episodic major depression. *Journal of Abnormal Psychology, 104*(1), 132-139.

Loeber, R., & Farrington, D. P. (1998). *Serious and violent juvenile offenders: Risk factors and successful interventions*. Thousand Oaks, CA: Sage Publications, Inc.

Loman, M. M., & Gunnar, M. R. (2010). Early experience and the development of stress reactivity and regulation in children. *Neuroscience and Biobehavioral Reviews, 34*(6), 867-876.

Lomanowska, A. M., Lovic, V., Rankine, M. J., Mooney, S. J., Robinson, T. E., & Kraemer, G. W. (2011). Inadequate early social experience increases the incentive salience of reward-related cues in adulthood. *Behavioural Brain Research, 220*(1), 91-99.

Lomanowska, A. M., Rana, S. A., McCutcheon, D., Parker, L. A., & Wainwright, P. E. (2006). Artificial rearing alters the response of rats to natural and drug-mediated rewards. *Developmental Psychobiology, 48*(4), 301-314.

Lovic, V., & Fleming, A. S. (2004). Artificially-reared female rats show reduced prepulse inhibition and deficits in the attentional set shifting task-reversal of effects with maternal-like licking stimulation. *Behavioural Brain Research, 148*, 209-219.

Lovic, V., Keen, D., Fletcher, P. J., & Fleming, A. S. (2011a). Early-life maternal separation and social isolation produce and increase in impulsive action but not impulsive choice. *Behavioral Neuroscience, 125*(4), 481-491.

Lovic, V., Palombo, D. J., & Fleming, A. S. (2011b). Impulsive rats are less maternal. *Developmental Psychobiology, 53*(1), 13-22.

Lupien, S. J., King, S., Meaney, M. J., & McEwen, B. S. (2000). Child's stress hormone levels correlate with mother's socioeconomic status and depressive state. *Biological Psychiatry, 48*(10), 976-980.
Lynskey, M. T., Agrawal, A., & Heath, A. C. (2010). Genetically informative research on adolescent substance use: methods, findings, and challenges. *Journal of the American Academy of Child and Adolescent Psychiatry, 49*(12), 1202-1214.
Lyons-Ruth, K., Repacholi, B., & McLeod, S. S., E. (1991). Disorganized attachment behavior in infancy: short-term stability, maternal and infant correlates, and risk-related subtypes. *Development and Psychopathology, 3*(4), 377-396.
Macdonald, G., & Turner, W. L. (2008). Treatment foster care for improving outcomes in children and young people. *Cochrane Database of Systematic Reviews, 23*(1).
Macdonald, G. M., Higgins, J. P. T., & Ramchandani, P. (2006). Cognitive-behavioural interventions for children who have been sexually abused. *Cochrane Database of Systematic Reviews*(17054148).
MacLeod, J., & Nelson, G. (2000). Programs for the promotion of family wellness and the prevention of child maltreatment: a meta-analytic review. *Child Abuse and Neglect, 24*(11057701), 1127-1149.
MacMillan, H. L. (2000). Preventive health care, 2000 update: prevention of child maltreatment. *Canadian Medical Association Journal, 163*(11), 1451-1458.
MacMillan, H. L., MacMillan, J. H., Offord, D. R., Griffith, L., & MacMillan, A. (1994). Primary prevention of child sexual abuse: a critical review. Part II. *Journal of Child Psychology and Psychiatry and Allied Disciplines, 35*(7962245), 857-876.
MacMillan, H. L., Thomas, B. H., Jamieson, E., Walsh, C. A., Boyle, M. H., Shannon, H. S., & Gafni, A. (2005). Effectiveness of home visitation by public-health nurses in prevention of the recurrence of child physical abuse and neglect: a randomised controlled trial. *Lancet, 365*(15910951), 1786-1793.
MacMillan, H. L., Wathen, C. N., Barlow, J., Fergusson, D., M., Leventhal, J. M., & Taussig, H. N. (2009). Interventions to prevent child maltreatment and associate impairment. *Lancet, 373*(9659), 250-266.
Maestripieri, D. (2005). Early experience affects the intergenerational transmission of infant abuse in rhesus monkeys. *Proceedings of the National Academy of Sciences of the United States of America, 102*(27), 9726-9729.
Maestripieri, D., Higley, J. D., Lindell, S. G., Newman, T. K., McCormack, K. M., & Sanchez, M. M. (2006). Early maternal rejection affects the development of monoaminergic systems and adult abusive parenting in rhesus macaques (Macaca mulatta). *Behavioral Neuroscience, 120*(5), 1017-1024.
Maestripieri, D., Lindell, S. G., & Higley, J. D. (2007). Intergenerational transmission of maternal behavior in rhesus macaques and its underlying mechanisms. *Developmental Psychobiology, 49*(2), 165-171.
Marcus, S. M. (2009). Depression during pregnancy: rates, risks and consequences—Motherisk Update 2008. *Canadian Journal of Clinical Pharmacology, 16*(1), e15-22.
Marmorstein, N. R., Malone, S. M., & Iacono, W. G. (2004). Psychiatric disorders among offspring of depressed mothers: associations with paternal psychopathology. *American Journal of Psychiatry, 161*(9), 1588-1594.
Marmot Review Team. (2010). Fair society, healthy lives. The Marmot review. London, UK: University College of London Institute of Health Equity.
Martin, G., Bergen, H. A., Roeger, L., & Allison, S. (2004). Depression in young adolescents: investigations using 2 and 3 factor versions of the Parental Bonding Instrument. *Journal of Nervous and Mental Disease, 192*, 650-657.
Mâsse, L. C., & Tremblay, R. E. (1997). Behavior of boys in kindergarten and the onset of substance use during adolescence. *Archives of General Psychiatry, 54*(1), 62-68.
Massin, M. M., Withofs, N., Maeyns, K., & Ravet, F. (2001). The influence of fetal and postnatal growth on heart rate variability in young infants. *Cardiology, 95*(2), 80-83.
Maughan, B., & McCarthy, G. (1997). Childhood adversities and psychosocial disorders. *British Medical Bulletin, 53*(1), 156-169.
McCain, N., Mustard, F., & McCuaig, K. (2011). Early Years Study 3: making decisions, taking action. Toronto, ON: Margaret & Wallace McCain Family Foundation.
McCauley, J., Kern, D. E., Kolodner, K., Dill, L., Schreoder, A. F., DeChant, H. K., . . . Bass, E. B. (1997). Clinical characteristics of women with a history of childhood abuse: unhealed wounds. *JAMA: Journal of the American Medical Association, 277*(17), 1362-1368.
McCord, J., Tremblay, R. E., Vitaro, F., & Desmarais-Gervais, L. (1994). Boys' disruptive behavior, school adjustment, and delinquency: the Montreal Experiment. *International Journal of Behavioral Development, 17*(4), 739-752.

McDermott, J. F. (2011). The longitudinal study: a bridge to the future. *Journal of the American Academy of Child and Adolescent Psychiatry, 50*(4), 317-319.
McDermott, J. M., Perez-Edgar, K., Henderson, H. A., Chronis-Tuscano, A., Pine, D. S., & Fox, N. A. (2009). A history of childhood behavioral inhibition and enhanced response monitoring in adolescence are linked to clinical anxiety. *Biological Psychiatry, 65*(5), 445-448.
McEwen, B. S. (1998). Stress, adaptation, and disease: allostasis and allostatic load. *Annals of the New York Academy of Sciences, 840*, 33-44.
McEwen, B. S. (2003). Early life influences on life-long patterns of behavior and health. *Mental Retardation and Developmental Disabilities Research Reviews, 9*(3), 149-154.
McEwen, B. S., & Gianaros, P. J. (2010). Central role of the brain in stress and adaptation: links to socioeconomic status, health, and disease. *Annals of the New York Academy of Sciences, 1186*(1), 190-222.
McEwen, C., & Flouri, E. (2009). Fathers' parenting, adverse life events, and adolescents' emotional and eating disorder symptoms: the role of emotion regulation. *European Child and Adolescent Psychiatry, 18*(4), 206-216.
McGowan, P. O., Sasaki, A., D'Alessio, A. C., Dymov, S., Labonte, B., Szyf, M., . . . Meaney, M. (2009). Epigenetic regulation of the glucocorticoid receptor in human brain associates with childhood abuse. *Nature Neuroscience, 12*(3), 342-348.
McGowan, P. O., Sasaki, A., Huang, T. C., Unterberger, A., Suderman, M., Ernst, C., . . . Szyf, M. (2008). Promoter-wide hypermethylation of the ribosomal RNA gene promoter in the suicide brain. *PLoS ONE, 3*(5), e2085.
McGue, M., Elkins, I., & Iacono, W. G. (2000). Genetic and environmental influences on adolescent substance use and abuse. *American Journal of Medical Genetics, 96*(5), 671-677.
McGue, M., Osler, M., & Christensen, K. (2010). Causal inference and observational research: the utility of twins. *Perspectives on Psychological Science, 5*(5), 546-556.
McLoyd, V. C. (1998). Socioeconomic disadvantage and child development. *American psychologist, 53*(2), 185-204.
Meaney, M. (2011). [Human children and sequence variations in the genes].
Meaney, M. J. (2001). Maternal care, gene expression, and the transmission of individual differences in stress reactivity across generations. *Annual Review of Neuroscience, 24*, 1161-1192.
Meaney, M. J. (2010). Epigenetics and the biological definition of gene x environment interactions. *Child Development, 81*(20331654), 41-79.
Meaney, M. J., Liu, D., Caldji, C., Sharma, S., & Plotsky, P. M. (2000). Influence of neonatal rearing conditions on stress-induced adrenocorticotropin responses and norepinepherine release in the hypothalamic paraventricular nucleus. *Journal of Neuroendocrinology, 12*(1), 5-12.
Meaney, M. J., & Szyf, M. (2005). Maternal care as a model for experience-dependent chromatin plasticity? *Trends in Neurosciences, 28*(9), 456-463.
Mehler, M. F. (2008). Epigenetic principles and mechanisms underlying nervous system functions in health and disease. *Progress in Neurobiology, 86*(4), 305-341.
Mensah, F. K., & Hobcraft, J. (2008). Childhood deprivation, health and development: associations with adult health in the 1958 and 1970 British prospective birth cohort studies. *Journal of Epidemiology and Community Health, 62*(18559442), 599-606.
Meunier, J. C., Bisceglia, R., & Jenkins, J. M. (2012). Differential parenting and children's behavioral problems: curvilinear associations and mother-father combined effects. *Developmental Psychology, 48*(4), 987-1002.
Mikton, C., & Butchart, A. (2009). Child maltreatment prevention: a systematic review of reviews. *Bulletin of the World Health Organization, 87*(5), 353-361.
Mileva-Seitz, V., Kennedy, J., Atkinson, L., Steiner, M., Levitan, R., Matthews, S. G., . . . Fleming, A. S. (2011). Serotonin transporter allelic variation in mothers predicts maternal sensitivity, behavior and attitudes toward 6-month-old infants. *Genes, Brain, and Behavior, 10*(3), 325-333.
Mileva-Seitz, V., Steiner, M., Meaney, M., Atkinson, L., Levitan, R., Sokolowskii, M., & Fleming, A. (in press). Interaction between oxytocin (OXT) genotype and early experience predicts quality of mothering and postpartum mood. *PLoS ONE*.
Milgrom, J., & Westley, D. T. (2004). The mediating role of maternal responsiveness in some longer term effects of postnatal depression on infant development. *Infant Behavior and Development, 27*(4), 443.
Miller, G., Chen, E., & Cole, S. W. (2009). Health psychology: developing biologically plausible models linking the social world and physical health. *Annual Review of Psychology, 60*(19035829), 501-524.
Mills-Koonce, W. R., Garrett-Peters, P., Barnett, M., Granger, D. A., Blair, C., & Cox, M. J. (2011). Father contributions to cortisol responses in infancy and toddlerhood. *Developmental Psychology, 47*(2), 388-395.

Mitra, R., & Sapolsky, R. M. (2010a). Expression of chimeric estrogen-glucocorticoid-receptor in the amygdale reduces anxiety. *Brain Research, 1342*, 33-38.
Mitra, R., & Sapolsky, R. M. (2010b). Gene therapy in rodent amygdale against fear disorders. *Expert Opinion on Biological Therapy, 10*(9), 1289-1303.
Moehler, E., Biringen, Z., & Poustka, L. (2007). Emotional availability in a sample of mothers with a history of abuse. *American Journal of Orthopsychiatry, 77*(4), 624-628.
Moffitt, T. E. (1993). Adolescence-limited and life-course-persistent antisocial behavior: a developmental taxonomy. *Psychological Review, 100*(4), 674-701.
Moffitt, T. E., Arseneault, L., Belsky, D., Dickson, N., Hancox, R. J., Harrington, H., . . . al., e. (2011). A gradient of childhood self-control predicts health, wealth, and public safety. *Proceedings of the National Academy of Sciences of the United States of America, 108*(7), 2693-2698.
Moffitt, T. E., Caspi, A., Harrington, H., & Milne, B. J. (2002). Males on the life-course-persistent and adolescence-limited antisocial pathways: follow-up at age 26 years. *Development and Psychopathology, 14*(11893092), 179-207.
Moskvina, V., Farmer, A., Swainson, V., O'Leary, J., Gunasinghe, C., Owen, M., . . . Korszun, A. (2007). Interrelationship of childhood trauma, neuroticism, and depressive phenotype. *Depression and Anxiety, 24*(3), 163–168.
Msall, M. E., Bier, J. A., LaGasse, L., Tremont, M., & Lester, B. (1998). The vulnerable preschool child: the impact of biomedical and social risks on neurodevelopmental function. *Seminars in Pediatric Neurology, 5*(1), 52-61.
Mulcahy, M., & Trocmé, N. (2010). Children and youth in out-of-home care in Canada. CECW Information Sheet #78. Montreal, QC: Centre for Research on Children and Families, McGill University.
Murphy, D. L., & Lesch, K.-P. (2008). Targeting the murine serotonin transporter: insights into human neurobiology. *Nature Reviews Neuroscience, 9*(Feb), 85-96.
Murray, L., Wooglar, M., Murray, J., & Cooper, P. (2003). Self-exclusion from health care in women at high risk for postpartum depression. *Journal of Public Health Medicine, 25*(2), 131-137.
Nachmias, M., Gunnar, M., Mangelsdorf, S., Parritz, R. H., & Buss, K. (1996). Behavioral inhibition and stress reactivity: the moderating role of attachment security. *Child Development, 67*(2), 508-522.
Nagin, D. S., & Tremblay, R. E. (1999). Trajectories of boys' physical aggression, opposition, and hyperactivity on the path to physically violent and nonviolent juvenile delinquency. *Child Development, 70*(5), 1181-1196.
Nagin, D. S., & Tremblay, R. E. (2001). Analyzing developmental trajectories of distinct but related behaviors: a group-based method. *Psychological Methods, 6*(1), 18-34.
Nater, U. M., Whistler, T., Lonergan, W., Mletzko, T., Vernon, S. D., & Heim, C. (2009). Impact of acute psychosocial stress on peripheral blood gene expression pathways in healthy men. *Biological Psychology, 82*(2), 125-132.
National Human Genome Research Institute. Epigenomic marks [figure]. Retrieved August 19, 2012, from http://www.genome.gov/multimedia/illustrations/FactSheet_EpigenomicMechanisms.pdf
Neigh, G. N., Gillespie, C. F., & Nemeroff, C. B. (2009). The neurobiological toll of child abuse and neglect. *Trauma, Violence & Abuse, 10*(4), 389-410.
Nelson, C. A., Zeanah, C. H., Fox, N. A., Marshall, P. J., Smyke, A. T., & Guthrie, D. (2007). Cognitive recovery in socially deprived young children: the Bucharest Early Intervention Project. *Science, 318*(18096809), 1937-1940.
Nelson, E. E., Herman, K. N., Barrett, C. E., Noble, P. L., Wojteczko, K., Chisholm, K., . . . Pine, D. (2009). Adverse rearing experiences enhance responding to both aversive and rewarding stimuli in juvenile rhesus monkeys. *Biological Psychiatry, 66*(7), 702-704.
Nelson, H. D., Nygren, P., McInerney, Y., & Klein, J. (2004). Screening women and elderly adults for family and intimate partner violence: a review of the evidence for the U. S. Preventive Services Task Force. *Annals of Internal Medicine, 140*(14996681), 387-396.
Neppl, T. K., Conger, R. D., Scaramella, L. V., & Ontai, L. L. (2009). Intergenerational continuity in parenting behavior: mediating pathways and child effects. *Developmental Psychology, 45*(5), 1241-1256.
NICHD Early Child Care Research Network. (2002). Early child care and children's development prior to school entry: results from the NICHD study of early child care. *American Educational Research Journal, 39*(1), 133-164.
NICHD Early Child Care Research Network. (2005a). Early child care and children's development in the primary grades: follow-up results from the NICHD Study of Early Child Care. *American Educational Research Journal, 42*(3), 537-570.

NICHD Early Child Care Research Network. (2005b). Oral language and reading: reply to Bracken. *Developmental Psychology, 41*(6), 1000-1002.
NICHD Early Child Care Research Network. (2005c). Predicting individual differences in attention, memory, and planning in first graders from experiences at home, child care, and school. *Developmental Psychology, 41*(1), 99-114.
NICHD Early Child Care Research Network. (2006). The NICHD study of early child care and youth development: Findings for children up to age 4½ years *NIH Publication No. 05-4318*. Bethesda, MD: U.S. Department of Health and Human Services.
Nierop, A., Bratsikas, A., Zimmermann, R., & Ehlert, U. (2006). Are stress-induced cortisol changes during pregnancy associated with postpartum depressive symptoms? *Psychosomatic Medicine, 68*(6), 931-937.
Nolin, P., & Ethier, L. (2007). Using neuropsychological profiles to classify neglected children with or without physical abuse. *Child Abuse and Neglect, 31*(6), 631-643.
Nores, M., Belfield, C. R., Barnett, W. S., & Schweinhart, L. (2005). Updating the economic impacts of the High/Scope Perry preschool program. *Educational Evaluation and Policy Analysis, 27*(3), 245-261.
Numan, M., Fleming, A. S., & Levy, F. (2006). Maternal behavior. In J. D. Neill (Ed.), *Knobil and Neill's physiology of reproduction* (pp. 1921 – 1993). London, UK: Elsevier.
Numan, M., & Insel, T. R. (2003). *The neurobiology of parental beahvior: Hormones, brain, and behavior*. New York, NY: Springer.
O'Connor, S., Vietze, P. M., Sherrod, K. B., Sandler, H. M., & Altemeier, W. A. (1980). Reduced incidence of parenting inadequacy following rooming-in. *Pediatrics, 66*(7402802), 176-182.
O'Connor, T. G., Ben-Shlomo, Y., Heron, J., Golding, J., Adams, D., & Glover, V. (2005). Parenatal anxiety predicts individual differences in cortisol in pre-adolescent children. *Biological Psychiatry, 58*(3), 211-217.
Odgers, C. L., Caspi, A., Broadbent, J. M., Dickson, N., Hancox, R. J., Harrington, H., . . . Moffitt, T. E. (2007). Prediction of differential adult health burden by conduct problem subtypes in males. *Archives of General Psychiatry, 64*(4), 476-484.
Odgers, C. L., Moffitt, T. E., Broadbent, J. M., Dickson, N., Hancox, R. J., Harrington, H., . . . Caspi, A. (2008). Female and male antisocial trajectories: from childhood origins to adult outcomes. *Development and Psychopathology, 20*(2), 673-716.
Odgers, C. L., Moffitt, T. E., Tach, L. M., Sampson, R. J., Taylor, A., Matthews, C. L., & Caspi, A. (2009). The protective effects of neighborhood collective efficacy on British children growing up in deprivation: a developmental analysis. *Developmental Psychology, 45*(4), 942-957.
Offord Centre for Child Studies. School Readiness to Learn Project. Retrieved June 1, 2012, from http://www.offordcentre.com/readiness/
Olds, D., Henderson, C. R., Cole, R., Eckenrode, J., Kitzman, H., Luckey, D., . . . Powers, J. (1998). Long-term effects of nurse home visitation on children's criminal and antisocial behavior: 15-year follow-up of a randomized controlled trial. *JAMA: Journal of the American Medical Association, 280*(9786373), 1238-1244.
Olds, D. L., Eckenrode, J., Henderson, C. R., Jr., Kitzman, H., Powers, J., Cole, R., . . . Luckey, D. (1997). Long-term effects of home visitation on maternal life course and child abuse and neglect. Fifteen-year follow-up of a randomized trial. *JAMA: Journal of the American Medical Association, 278*(8), 637-643.
Olds, D. L., Henderson, C. R., Chamberlin, R., & Tatelbaum, R. (1986). Preventing child abuse and neglect: a randomized trial of nurse home visitation. *Pediatrics, 78*(2425334), 65-78.
Olds, D. L., Kitzman, H., Hanks, C., Cole, R., Anson, E., Sidora-Arcoleo, K., . . . Bondy, J. (2007a). Effects of nurse home visiting on maternal and child functioning: age-9 follow-up of a randomized trial. *Pediatrics, 120*(17908740), 832-845.
Olds, D. L., Robinson, J., O'Brien, R., Luckey, D. W., Pettitt, L. M., Henderson, C. R., . . . Talmi, A. (2002). Home visiting by paraprofessionals and by nurses: a randomized, controlled trial. *Pediatrics, 110*(12205249), 486-496.
Olds, D. L., Robinson, J., Pettitt, L., Luckey, D. W., Holmberg, J., Ng, R. K., . . . Henderson, C. R. (2004). Effects of home visits by paraprofessionals and by nurses: age 4 follow-up results of a randomized trial. *Pediatrics, 114*(15574615), 1560-1568.
Olds, D. L., Sadler, L., & Kitzman, H. (2007b). Programs for parents of infants and toddlers: recent evidence from randomized trials. *Journal of Child Psychology and Psychiatry, 48*(3-4), 355-391.
Opler, M. G., & Susser, E. S. (2005). Fetal environment and schizophrenia. *Environmental Health Perspectives, 113*(9), 1239-1242.

Ouellet-Morin, I., Boivin, M., Dionne, G., Lupien, S. J., Arseneault, L., Barr, R. G., . . . Tremblay, R. E. (2008). Variations in heritability of cortisol reactivity to stress as a function of early familial adversity among 19-month-old twins. *Archives of General Psychiatry, 65*(2), 211-218.

Ouellet-Morin, I., Dionne, G., Perusse, D., Lupien, S. J., Arseneault, L., Barr, R. G., . . . Boivin, M. (2009). Daytime cortisol secretion in 6-month-old twins: genetic and environmental contributions as a function of early familial adversity. *Biological Psychiatry, 65*(5), 409-416.

Panthangi, V., West, P., Savoy-Moore, R. T., Geeta, M., & Reickert, E. (2009). Is seasonal variation another risk factor for postpartum depression? *Journal of the American Board of Family Medicine, 22*(5), 492-497.

Paris, R., Bolton, R. E., & Weinberg, M. K. (2009). Postpartum depression, suicidality, and mother-infant interactions. *Archives of Women's Mental Health, 12*(5), 309-321.

Patel, V., DeSouza, N., & Rodrigues, M. (2003). Postnatal depression and infant growth and development in low income countries: a cohort study from Goa, India. *Archives of Disease in Childhood, 88*(1), 34-37.

Patterson, G. R., Capaldi, D., & Bank, L. (1991). An early starter model for predicting delinquency. In K. H. Rubin & D. J. Pepler (Eds.), *Development and Treatment of Childhood Aggression* (pp. 139-168). London, UK: Psychology Press.

Patterson, G. R., Reid, J. B., & Eddy, J. M. (2002). A brief history of the Oregon model. In J. B. Reid, G. R. Patterson & J. Snyder (Eds.), *Antisocial behavior in children and adolescents: A developmental analysis and model for intervention* (pp. 3-21). Washington, DC: American Psychological Association.

Pears, K. C., & Fisher, P. A. (2005). Emotion understanding and theory of mind among maltreated children in foster care: evidence of deficits. *Developmental Psychopathology, 17*(1), 47-65.

Pears, K. C., Kim, H. K., & Fisher, P. A. (2008). Psychosocial and cognitive functioning of children with specific profiles of maltreatment. *Child Abuse and Neglect, 32*(10), 958-971.

Peisner-Feinberg, E. S., Burchinal, M. R., Clifford, R. M., Culkin, M. L., Howes, C., Kagan, S. L., & Yazejian, N. (2001). The relation of preschool child-care quality to children's cognitive and social developmental trajectories through second grade. *Child Development, 72*(5), 1534-1553.

Penza, K. M., Heim, C., & Nemeroff, C. B. (2003). Neurobiological effects of childhood abuse: implications for the pathophysiology of depression and anxiety. *Archives of Women's Mental Health, 6*(1), 15-22.

Perusse, D., Neale, M. C., Heath, A. C., & Eaves, L. J. (1994). Human parental behavior: evidence for genetic influence and potential implication for gene-culture transmission. *Behavior Genetics, 24*(4), 327-335.

Petitclerc, A., Boivin, M., Dionne, G., Zoccolillo, M., & Tremblay, R. E. (2009). Disregard for rules: The early development and predictors of a specific dimension of disruptive behavior disorders. *Journal of Child Psychology and Psychiatry and Allied Disciplines, 50*(12), 1477-1484.

Petitclerc, A., & Tremblay, R. E. (2009). Childhood disruptive behaviour disorders: Review of their origin, development, and prevention. *Les troubles de comportement perturbateur de l'enfance : une revue deleur origine, de leur développement et de la prévention., 54*(4), 222-231.

Pierce, T., Boivin, M., Frenette, É., Forget-Dubois, N., Dionne, G., & Tremblay, R. E. (2010). Maternal self-efficacy and hostile-reactive parenting from infancy to toddlerhood. *Infant Behavior and Development, 33*(2), 149-158.

Pollak, S. D. (2005). Early adversity and mechanisms of plasticity: integrating affective neuroscience with developmental approaches to psychopathology. *Developmental Psychopathology, 17*(3), 735-752.

Pollak, S. D. (2008). Mechanisms linking early experience and the emergence of emotions: illustrations from the study of maltreated children. *Current Directions in Psychological Science, 17*(6), 370-375.

Pollak, S. D., Cicchetti, D., Klorman, R., & Brumaghim, J. T. (1997). Cognitive brain event-related potentials and emotion processing in maltreated children. *Child Development, 68*, 773-787.

Pollak, S. D., Klorman, R., Thatcher, J. E., & Cicchetti, D. (2001). P3b reflects maltreated children's reactions to facial displays of emotion. *Psychophysiology, 38*(2), 267-274.

Prinz, R. J., Sanders, M. R., Shapiro, C. J., Whitaker, D. J., & Lutzker, J. R. (2009). Population-based prevention of child maltreatment:the U.T. Triple p system population trial. *Prevention Science, 10*, 1-12.

Putnam, F. W. (2003). Ten-year research update review: Child sexual abuse. *Journal of the American Academy of Child & Adolescent Psychiatry, 42*(3), 269-278.

Quinton, D., & Rutter, M. (1984a). Parents with children in care--I. Current circumstances and parenting. *Journal of Child Psychology and Psychiatry and Allied Disciplines, 25*(2), 211-229.

Quinton, D., & Rutter, M. (1984b). Parents with children in care--II. Intergenerational continuities. *Journal of Child Psychology and Psychiatry and Allied Disciplines, 25*(2), 231-250.

Ramchandani, P., & Jones, D. P. H. (2003). Treating psychological symptoms in sexually abused children: from research findings to service provision. *British Journal of Psychiatry, 183*(14645018), 484-490.

Ramchandani, P., Stein, A., Evans, J., & O'Connor, T. G. (2005). Paternal depression in the postnatal period and child development: a prospective population study. *Lancet, 365*(9478), 2201-2205.
Ramchandani, P. G., Stein, A., Hotopf, M., & Wiles, N. J. (2006). Early parental and child predictors of recurrent abdominal pain at school age: results of a large population-based study. *Journal of the American Academy of Child and Adolescent Psychiatry, 45*(6), 729-736.
Ramey, C. T., Campbell, F. A., Burchinal, M., Skinner, M. L., Gardner, D. M., & Ramey, S. L. (2000). Persistent effects of early childhood education on high-risk children and their mothers. *Applied Developmental Science, 4*(1), 2-14.
Rao, U., Hammen, C., Ortiz, L. R., Chen, L., & Poland, R. E. (2008). Effects of early and recent adverse experiences on adrenal response to psychosocial stress in depressed adolescents. *Biological Psychiatry, 64*(6), 521-526.
Rebollo, A. G., & Montero, C. M. (2000). [Perinatal variables and health inequalities in a health-care district in Caceres, Spain]. *Gaceta Sanitaria, 14*(1), 31-38.
Reeb, B. T., Conger, K. J., & Wu, E. Y. (2010). Paternal depressive symptoms and adolescent functioning: the moderating effect of gender and father hostility. *Fathering, 8*(1), 131-142.
Rees, S. L., Panesar, S., Steiner, M., & Fleming, A. S. (2006). The effects of adrenalectomy and corticosterone replacement on induction of maternal behavior in the virgin female rat. *Hormones and Behavior, 49*(3), 337-345.
Reid, M. J., Webster-Stratton, C., & Beauchaine, T. (2001). Parent training in Head Start: A comparison of program response among African American, Asian American, Caucasian, and Hispanic mothers. *Prevention Science, 2*(4), 209-227.
Relton, C. L., & Smith, G. D. (2010). Epigenetic epidemiology of common complex disease: prospects for prediction, prevention, and treatment. *Plos Medicine, 7*(10).
Repetti, R. L., Taylor, S. E., & Seeman, T. E. (2002). Risky families: family social environments and the mental and physical health of offspring. *Psychological Bulletin, 128*(2), 330-366.
Resnick, L. B. (1985). Education and learning to think: Subcommittee report. Washington, DC: National Research Council Commission on Behavioral and Social Sciences and Education.
Rey, J. M. (1995). Perceptions of poor maternal care are associated with adolescent depression. *Journal of Affective Disorders, 34*(2), 95-100.
Reynolds, A., Walberg, H., & Weissberg, R. (2002). Review of 'Promoting positive outcomes: issues in children's and families' lives'. *Adolescence, 37*(148), 866.
Reynolds, A. J., Mathieson, L. C., & Topitzes, J. W. (2009). Do early childhood interventions prevent child maltreatment? A review of research. *Child Maltreatment, 14*(2), 182-206.
Reynolds, A. J., Temple, J. A., Ou, S.-R., Arteaga, I. A., & White, B. A. B. (2011a). School-based early childhood education and age-28 well-being: effects by timing, dosage, and subgroups. *Science, 333*(6040), 360-364.
Reynolds, A. J., Temple, J. A., Ou, S.-R., Robertson, D. L., Mersky, J., Topitzes, J. W., & Niles, M. D. (2007). Effects of a school-based, early childhood intervention on adult health and well-being: a 19-year follow-up of low-income families. *Archives of Pediatrics and Adolescent Medicine, 161*(8), 730-739.
Reynolds, A. J., Temple, J. A., White, B. A. B., Ou, S.-R., & Robertson, D. L. (2011b). Age 26 cost–benefit analysis of the child-parent center early education program. *Child Development, 82*(1), 379-404.
Richter, L. (2004). The importance of caregiver child interactions for the survival and healthy development of young children: A review. Geneva, Switzerland: WHO, Department of Child and Adolescent Health and Development.
Righetti-Veltema, M., Conne-Perréard, E., Bousquet, A., & Manzano, J. (2002). Postpartum depression and mother-infant relationship at 3 months old. *Journal of Affective Disorders, 70*(3), 291-306.
Rikhye, K., Tyrka, A. R., Kelly, M. M., Gagne, G. G., Mello, A. F., Mello, M. F., . . . Carpenter, L. L. (2008). Interplay between childhood maltreatment, parental bonding, and gender effects: Impact on quality of life. *Child Abuse and Neglect, 32*(1), 19-34.
Rispens, J., Aleman, A., & Goudena, P. P. (1997). Prevention of child sexual abuse victimization: a meta-analysis of school programs. *Child Abuse and Neglect, 21*(9330798), 975-987.
Roberts, R., O'Connor, T., Dunn, J., Golding, J., & ALSPAC Study Team. (2004). The effects of child sexual abuse in later family life: mental health, parenting and adjustment of offspring. *Child Abuse and Neglect, 28*(5), 525-545.
Rogers, M. A., Kasai, K., Koji, M., Fukuda, I., A., Nakagome, K., Fukuda, M., & Kato, N. (2004). Executive and prefrontal dysfunction in unipolar depression: a review of neuropsychological and imaging evidence. *Neurosciences Research, 50*(1), 1-11.

Rose, R. J., Dick, D. M., Viken, Rj, & Kaprio, J. (2001). Gene-environment interaction in patterns of adolescent drinking: regional residency moderates longitudinal influences on alcohol use. *Alcoholism, Clinical and Experimental Research, 25*(5), 637-643.
Roseboom, T. J., van der Meulen, J. H., Osmond, C., Barker, D. J., Ravelli, A. C., Schroeder-Tanka, J. M., . . . Bleker, O. P. (2000). Coronary heart disease after prenatal exposure to the Dutch famine, 1944-45. *Heart, 84*(6), 595-598.
Rosenblum, L. A., Coplan, J. D., Friedman, S., Bassoff, T., Gorman, J. M., & Andrews, M. W. (1994). Adverse early experiences affect nonadrenergic and serotonergic functioning in adult primates. *Biological Psychiatry, 35*(4), 221-227.
Rosenblum, L. A., Smith, E. L., Altemus, M., Scharf, B. A., Owens, M. J., Nemeroff, C. B., . . . Coplan, J. D. (2002). Differing concentrations of corticotropin-releasing factor and oxytocin in the cerebrospinal fluid of bonnet and pigtail macques. *Psychoneuroendocrinology, 27*(6), 651-660.
Roth, T. L., Lubin, F. D., Funk, A. J., & Sweatt, J. D. (2009). Lasting epigenetic influence of early-life adversity on the BDNF gene. *Biological Psychiatry, 65*(9), 760-769.
Roth, T. L., & Sweatt, J. D. (2010). Epigenetic marking of the BDNF gene by early-life adverse experiences. *Hormones and Behavior, 59*(3), 315-320.
Runyan, D. K. (2008). The challenges of assessing the incidence of inflicted traumatic brain injury: a world perspective. *American journal of preventive medicine, 34*(4), S112.
Runyan, D. K., & Gould, C. L. (1985). Foster care for child maltreatment: impact on delinquent behavior. *Pediatrics, 75*(3975127), 562-568.
Russell, B. S., Trudeau, J., & Britner, P. A. (2008). Intervention type matters in primary prevention of abusive head injury: event history analysis results. *Child Abuse and Neglect, 32*(18990448), 949-957.
Rutter, M. (2007). Proceeding from observed correlation to causal inference: the use of natural experiments. *Perspectives on Psychological Science, 2*(4), 377-395.
Rutter, M., Beckett, C., Castle, J., Colvert, E., Kreppner, J., Mehta, M., . . . Sonuga-Barke, E. (2007). Effects of profound early institutional deprivation: an overview of findings from a UK longitudinal study of Romanian adoptees. *European Journal of Developmental Psychology, 4*(3), 332-350.
Rutter, M., Moffitt, T. E., & Caspi, A. (2006). Gene-environment interplay and psychopathology: multiple varieties but real effects. *Journal of Child Psychology and Psychiatry and Allied Disciplines, 47*(3-4), 226-261.
Rutter, M., Sonuga-Barke, E. J., & Castle, J. (2010). Investigating the impact of early institutional deprivation on development: background and research strategy of the English and Romanian Adoptees (ERA) study. *Monographs of the Society for Research in Child Development, 75*(1), 1-20.
Rutter, M., Thapar, A., & Pickles, A. (2009). Gene-environment interactions: biologically valid pathway or artifact? *Archives of General Psychiatry, 66*(12), 1287-1289.
Sameroff, A. J., & Seifer, R. (1983). Familial risk and child competence. *Child Development, 54*(5), 1254-1268.
Sampson, R. J., Raudenbush, S. W., & Earls, F. (1997). Neighborhoods and violent crime: a multilevel study of collective efficacy. *Science, 277*(5328), 918-924.
Sanders, M. R., Pidgeon, A. M., Gravestock, F., Connors, M. D., Brown, S., & Young, R. W. (2004). Does parental attributional retraining and anger management enhance the effects of the triple P-positive parenting program with parents at risk of child maltreatment? *Behavior Therapy, 35*(3), 513-535.
Sapolsky, R. M. (1996). Why stress is bad for your brain. *Science, 273*(5276), 749-750.
Sapolsky, R. M., Romero, L. M., & Munck, A. U. (2000). How do glucocorticoids influence stress responses? Integrating permissive, suppressive, stimulatory, and preparative actions. *Endocrine Reviews, 21*(1), 55-89.
Sarkadi, A., Kristiansson, R., Oberklaid, F., & Bremberg, S. (2008). Fathers' involvement and children's developmental outcomes: a systematic review of longitudinal studies. *Acta Paediatrica, 97*(2), 153-158.
Scaramella, L. V., Neppl, T. K., Ontai, L. L., & Conger, R. D. (2008). Consequences of socioeconomic disadvantage across three generations: parenting behaviour and child externalizing problems. *Journal of Family Psychology, 22*(5), 725-733.
Schmitt, J. E., Lenroot, R. K., Wallace, G. L., Ordaz, S., Taylor, K. N., Kabani, N., . . . Giedd, J. N. (2008). Identification of genetically mediated cortical networks: a multivariate study of pediatric twins and siblings. *Cerebral Cortex, 18*(8), 1737-1747.
Schreuder, M. F., Fodor, M., van Wijk, J. A., & Delemarre-van de Waal, H. A. (2006). Association of birth weight with cardiovascular parameters in adult rats during baseline and stressed conditions. *Pediatric Research, 59*(1), 126-130.
Seeman, T. E., Singer, B. H., Ryff, C. D., Dienberg Love, G., & Levy-Storms, L. (2002). Social relationships, gender, and allostatic across two age cohorts. *Psychosomatic Medicine, 64*(3), 395-406.

Seifritz, E., Esposito, F., Neuhoff, J. G., Luthi, A., Mustovic, H., Dammann, G., . . . Di Salle, F. (2003). Differential sex-independent amygdala response to infant crying and laughing in parents versus nonparents. *Biological Psychiatry, 54*(12), 1367-1375.

Shackman, J. E., Shackman, A. J., & Pollak, S. D. (2007). Physical abuse amplifies attention to threat and increases anxiety in children. *Emotion, 7*(4), 838-852.

Shankaran, S., Das, A., Bauer, C. R., Bada, H., Lester, B., Wright, L., & Higgins, R., & Poole, K. (2006). Fetal origin of childhood disease: intrauterine growth restriction in term infants and risk for hypertension at 6 years of age. *Archives of Pediatrics and Adolescent Medicine, 160*(9), 977-981.

Sheridan, J. F., Stark, J. L., Avitsur, R., & Padgett, D. A. (2000). Social disruption, immunity, and susceptibility to viral infection - Role of glucocorticoid insensitivity and NGF. *Neuroimmunomodulation, 917*, 894-905.

Sheridan, M. A., Sarsour, K., Jutte, D., D'Esposito, M., & Boyce, W. T. (2012). The impact of social disparity on prefrontal function in childhood. *PLoS ONE, 7*(4), e35744.

Shin, S. H., Edwards, E. M., & Heeren, T. (2009). Child abuse and neglect: relations to adolescent binge drinking in the national longitudinal study of Adolescent Health (AddHealth) Study. *Addictive Behaviors, 34*(19028418), 277-280.

Shonkoff, J. P., Boyce, W. T., & McEwen, B. S. (2009). Neuroscience, molecular biology, and the childhood roots of health disparities building a new framework for health promotion and disease prevention. *JAMA: Journal of the American Medical Association, 301*(21), 2252-2259.

Shonkoff, J. P., & Philips, D. (Eds.). (2000). *From neurons to neighborhoods: The science of early childhood development*. Washington, DC: National Academies Press.

Siddiqi, A., Irwin, L. G., & Hertzman, C. (2007). Total Environment Assessment Model for early child development (World Health Organization's Commission on the Social Determinants of Health). Vancouver, BC: University of British Columbia, Human Early Learning Partnership.

Siegel, E., Bauman, K. E., Schaefer, E. S., Saunders, M. M., & Ingram, D. D. (1980). Hospital and home support during infancy: impact on maternal attachment, child abuse and neglect, and health care utilization. *Pediatrics, 66*(7402803), 183-190.

Silverman, W. K., Ortiz, C. D., Viswesvaran, C., Burns, B. J., Kolko, D. J., Putnam, F. W., & Amaya-Jackson, L. (2008). Evidence-based psychosocial treatments for children and adolescents exposed to traumatic events. *Journal of Clinical Child and Adolescent Psychology, 37*(18444057), 156-183.

Sinha, V., Trocmé, N., Fallon, B., MacLaurin, B., Fast, E., Prokop, S. T., . . . Richard, K. (2011). Kiskisik Awasisak: Remember the children. Understanding the overrepresentation of First Nations children in the child welfare system. Ottawa, ON: Assembly of First Nations.

Skeer, M., McCormick, M. C., Normand, S. L. T., Buka, S. L., & Gilman, S. E. (2009). A prospective study of familial conflict, psychological stress, and the development of substance use disorders in adolescence. *Drug and Alcohol Dependence, 104*(1-2), 65-72.

Skowron, E., & Reinemann, D. H. S. (2005). Effectiveness of psychological interventions for child maltreatment: a meta-analysis. *Psychotherapy, 42*(1), 52-71.

Slutske, W. S., Zhu, G., Meier, M. H., & Martin, N. G. (2010). Genetic and environmental influences on disordered gambling in men and women. *Archives of General Psychiatry, 67*(6), 624-630.

Sokolowski, M. B. (2001). Drosophila: genetics meets behaviour. *Nature Reviews Genetics, 2*, 879-890.

Sokolowski, M. B., & Wahlsten, D. (2001). Gene-environment interaction and complex behavior *Methods in Genomic Neuroscience.* : S. O. Moldin, CRC Press.

Sokolowski, M. B. C., Disma, G., & Abramson, C. I. (2010). A paradigm for operant conditioning in blow flies ("Phormia Terrae Novae" Robineau-Desvoidy, 1830). *Journal of the Experimental Analysis of Behavior, 93*(1), 81-89.

Spertus, I. L., Yehuda, R., Wong, C. M., Halligan, S., & Seremetis, S. V. (2003). Childhood emotional abuse and neglect as predictors of psychological and physical symptoms in women presenting to a primary care practice. *Child Abuse and Neglect, 27*(11), 1247-1258.

Spoth, R. L., Redmond, C., & Shin, C. (2001). Randomized trial of brief family interventions for general populations: adolescent substance use outcomes 4 years following baseline. *Journal of Consulting and Clinical Psychology, 69*(4), 627-642.

Stallard, P. (2006). Psychological interventions for post-traumatic reactions in children and young people: a review of randomised controlled trials. *Clinical Psychology Review, 26*(16481081), 895-911.

Stallings, J., Fleming, A. S., Corter, C., Worthman, C., & Steiner, M. (2001). The effects of infant cries and odors on sympathy, cortisol, and autonomic responses in new mothers and nonpostpartum women. *Parenting: Science and Practice, 1*(1/2), 71.

Steptoe, A., & Marmot, M. (2002). The role of psychobiological pathways in socio-economic inequalities in cardiovascular disease risk. *European Heart Journal, 23*, 13-25.
Storey, A. E., Noseworthy, D. E., Delahunty, K. M., Halfyard, S. J., & McKay, D. W. (2011). The effects of social context on the hormonal and behavioral responsiveness of human fathers. *Hormones and Behavior, 60*(4), 353-361.
Storey, A. E., Walsh, C. J., Quinton, R. L., & Wynne-Edwards, K. E. (2000). Hormonal correlates of paternal responsiveness in new and expectant fathers. *Evolution and human behavior : official journal of the Human Behavior and Evolution Society, 21*(2), 79-95.
Stover, C. S., Connell, C. M., Leve, L. D., Neiderhiser, J. M., Shaw, D. S., Scaramella, L. V., . . . Reiss, D. (2012). Fathering and mothering in the family system: linking marital hostility and aggression in adopted toddlers. *Journal of Child Psychology and Psychiatry and Allied Disciplines, 53*(4), 401-409.
Sullivan, C. M., & Bybee, D. I. (1999). Reducing violence using community-based advocacy for women with abusive partners. *Journal of Consulting and Clinical Psychology, 67*(1), 43-53.
Sullivan, C. M., Bybee, D. I., & Allen, N. E. (2002). Findings from a community-based program for battered women and their children. *Journal of Interpersonal Violence, 17*(9), 915-936.
Suomi, S. J. (1999). Attachment in rhesus monkeys. In J. Cassidy & P. R. Shaver (Eds.), *Handbook of attachment: theory, research, and clinical applications* (pp. 181-197). New York, NY: Guilford Press.
Suomi, S. J. (2006). Risk, resilience, and gene x environment interactions in rhesus monkeys. *Annals of the New York Academy of Sciences, 1094*, 52-62.
Surtees, P. G., & Wainwright, N. W. (2007). The shackles of misfortune: social adversity assessment and representation in a chronic-disease epidemiological setting. *Social Science and Medicine, 64*(1), 95-111.
Swain, J. E. (2008). Baby stimuli and the parent brain: functional neuroimaging of the neural substrates of parent-infant attachment. *Psychiatry, 5*(8), 28–36.
Swain, J. E., & Hoa, S. S. (2010). Baby smile response circuits of the parental brain. *Behavioral and Brain Sciences, 33*, 460-461.
Syme, S. L., & Berkman, L. F. (1976). Social class, susceptibility and sickness. *American Journal of Epidemiology, 10*(1), 1-8.
Szyf, M., McGowan, P., & Meaney, M. J. (2008). The social environment and the epigenome. *Environmental and Molecular Mutagenesis, 49*(1), 46-60.
Szyf, M., Weaver, I. C., Champagne, F. A., Diorio, J., & Meaney, M. J. (2005). Maternal programming of steroid receptor expression and phenotype through DNA methylation in the rat. *Frontiers in Neuroendocrinology, 26*(3-4), 139-162.
Takahashi, H., Takahashi, K., & Liu, F.-C. (2010). FOXP genes, neural development, speech and language disorders forkhead transcription factors. In K. Maiese (Ed.), (Vol. 665, pp. 117-129). New York, NY: Springer.
Talvik, I., Alexander, R. C., & Talvik, T. (2008). Shaken baby syndrome and a baby's cry. *Acta Paediatrrica, 97*(18397351), 782-785.
Tamis-Lemonda, C. S., & Bornstein, M. H. (1989). Habituation and maternal encouragement of attention in infancy as predictors of toddler language, play, and representational competence. *Child Development, 60*(3), 738-751.
Tamis-Lemonda, C. S., Bornstein, M. H., & Baumwell, L. (2001). Maternal responsiveness and children's achievement of language milestones. *Child Development, 72*(3), 748-767.
Tamis-LeMonda, C. S., Shannon, J. D., Cabrera, N. J., & Lamb, M. E. (2004). Fathers and mothers at play with their 2- and 3-year-olds: contributions to language and cognitive development. *Child Development, 75*(6), 1806-1820.
Taussig, H.N., Clyman, R.B., Landsverk, J.,(2001) Children who return home from foster care: A six-year prospective study of behavioral health outcomes in adolescence. Pediatrics 2001; 108(1):e10.
Taylor, A., & Kim-Cohen, J. (2007). Meta-analysis of gene-environment interactions in developmental psychopathology. *Development and Psychopathology, 19*(4), 1029-1037.
Taylor, D. K., & Beauchamp, C. (1988). Hospital-based primary prevention strategy in child abuse: a multi-level needs addressment. *Child Abuse and Neglect, 12*(3167622), 343-354.
Teicher, M. H., Andersen, S. L., Polcari, A., Anderson, C. M., Navalta, C. P., & Kim, D. M. (2003). The neurobiological consequences of early stress and childhood maltreatment. *Neuroscience and Biobehavioral Reviews, 27*(1-2), 33-44.
Temple, J. A., & Reynolds, A. J. (2007). Benefits and costs of investments in preschool education: evidence from the Child–Parent Centers and related programs. *Economics of Education Review, 26*(1), 126-144.

Terling, T. (1999). The efficacy of family reunification practices: reentry rates and correlates of reentry for abused and neglected children reunited with their families. *Child Abuse and Neglect, 23*(10626617), 1359-1370.
The Adverse Childhood Experiences Study. What is The ACE Study? Retrieved August 19, 2012, from http://www.acestudy.org
Theodore, A. D., Chang, J. J., Runyan, D. K., Hunter, W. M., Bangdiwala, S. I., & Agans, R. (2005). Epidemiologic features of the physical and sexual maltreatment of children in the Carolinas. *Pediatrics, 115*(15741359), 331-337.
Thoburn, J. (2007). Globalisation and child welfare: some lessons from a cross-national study of children in out-of-home care. *Social Work Monographs, 228*, 1-70.
Thomas, C., Hypponen, E., & Power, C. (2008). Obesity and type 2 diabetes risk in midadult life: the role of childhood adversity. *Pediatrics, 121*(5), e1240-1249.
Thomas, R., & Zimmer-Gembeck, M. J. (2007). Behavioral outcomes of Parent-Child Interaction Therapy and Triple P-Positive Parenting Program: a review and meta-analysis. *Journal of Abnormal Child Psychology, 35*(3), 475-495.
Tikkanen, R., Sjoberg, R. L., Ducci, F., Goldman, D., Holi, M., Tiihonen, J., & Virkkunen, M. (2009). Effects of MAOA-genotype, alcohol consumption, and aging on violent behavior. *Alcoholism, Clinical and Experimental Research, 33*(3), 428-434.
Tiwari, A., Leung, W. C., Leung, T. W., Humphreys, J., Parker, B., & Ho, P. C. (2005). A randomised controlled trial of empowerment training for Chinese abused pregnant women in Hong Kong. *British Journal of Obstetrics and Gynaecology, 112*(9), 1249-1256.
Tollenaar, M. S., Beijers, R., Jansen, J., Riksen-Walraven, J. M. A., & de Weerth, C. (2011). Maternal prenatal stress and cortisol reactivity to stressors in human infants. *Stress, 14*(1), 53-65.
Tomarken, A. J., Dichter, G. S., Garber, J., & Simien, C. (2004). Resting frontal brain activity: linkages to maternal depression and socio-economic status among adolescents. *Biological Psychology, 67*(1-2), 77-102.
Toth, S. L., Maughan, A., Manly, J. T., Spagnola, M., & Cicchetti, D. (2002). *The relative efficacy of two interventions in altering maltreated preschool children's representational models: implications for attachment theory* (Vol. 14). Cambridge, UK: Cambridge University Press.
Tremblay, R. E. (2000). The development of aggressive behaviour during childhood: What have we learned in the past century? *International Journal of Behavioral Development, 24*(2), 129-141.
Tremblay, R. E., Nagin, D. S., Séguin, J. R., Zoccolillo, M., Zelazo, P. D., Boivin, M., & Japel, C. (2005). Physical aggression during early childhood: trajectories and predictors. *Canadian Child and Adolescent Review, 14*(1), 3-9.
Tremblay, R. E., Phil, R. O., Vitaro, F., & Dobkin, P. L. (1994). Predicting early onset of male antisocial behavior from preschool behavior. *Archives of General Psychiatry, 51*(9), 732-739.
Trocmé, N., Fallon, B., MacLaurin, B., Sinha, V., Black, T., Fast, E., . . . Holroyd, J. (2010). Canadian Incidence Study of Reported Child Abuse and Neglect – 2008: Executive Summary. Ottawa, ON: Public Health Agency of Canada.
Trocmé, N., Shlonsky, A., Mulcahy, M., & Esposito, T. (2009). *National outcomes matrix: Core indicators*. Paper presented at the Second National Roundtable on Child Welfare Outcomes, Montreal, QC.
Tronick, E., & Reck, C. (2009). Infants of depressed mothers. *Harvard Review of Psychiatry, 17*(2), 147-156.
Turkheimer, E. (2011). Commentary: variation and causation in the environment and genome. *International Journal of Epidemiology, 40*(3), 598-601.
Turkheimer, E., & Gottesman, I. L. (1996). Simulating the dynamics of genes and environment in development. *Development and Psychopathology, 8*(4), 667-677.
U.S. Department of Health and Human Services, & Administration for Children and Families. (2010). Child maltreatment 2009. Washington, DC: DHHS.
Udwin, O. (1983). Imaginative play training as an intervention method with institutionalised preschool children. *British Journal of Educational Psychology, 53*(1), 32-39.
Uher, R., & McGuffin, P. (2010). The moderation by the serotonin transporter gene of environmental adversity in the etiology of depression: 2009 update. *Molecular Psychiatry, 15*(1), 18-22.
Ungar, M. (2006). Nurturing hidden resilience in at-risk youth in different cultures. *Journal of the Canadian Academy of Child and Adolescent Psychiatry, 15*(2), 53-58.
Ungar, M., & Liebenberg, L. (2005). The International Resilience Project: A mixed
methods approach to the study of resilience across cultures. In M. Ungar (Ed.), *Handbook for working with children and youth: Pathways to resilience across cultures and contexts* (pp. 211-226). Thousand Oaks, CA: Sage.

UNICEF. (2007). *State of the world's children 2007: Women and children: the double dividend of gender equality*. New York, NY: United Nations Children's Fund (UNICEF).
United Nations. (1991). No. 27531. Convention on the rights of the child. Adopted by the General Assembly of the United Nations on 20 November 1989. New York, NY: UN.
United Nations. (2005). General Comment No. 7: Implementing Child Rights in early childhood. . Geneva, Switzerland: UN Office of the United Nations High Commission for Human Rights Committee on the Rights of the Child (CRC).
United Nations, & Office of the United Nations High Commission for Human Rights (CRC). (1990). Convention on the Rights of the Child, . Retrieved from http://www2.ohchr.org/english/law/crc.htm
University of Otago. Christchurch Health & Development Study. Retrieved August 30, 2012, from http://www.otago.ac.nz/christchurch/research/healthdevelopment/index.html
Van Der Vegt, E. J. M., Van Der Ende, J., Ferdinand, R. F., Verhulst, F. C., & Tiemeier, H. (2009). Early childhood adversities and trajectories of psychiatric problems in adoptees: evidence for long lasting effects. *Journal of abnormal child psychology, 37*(2), 239-249.
Van Ijzendoorn, M. H., Bakermans-Kranenburg, M.J., & Mesman, J. (2008). Dopamine system genes associated with parenting in the context of daily hassles. *Genes, Brain, and Behavior, 7*(4), 403-410.
Van Lier, P., Boivin, M., Dionne, G., Vitaro, F., Brendgen, M., Koot, H., & Pérusse, D. (2007). Kindergarten children's genetic variabilities interact with friends' aggression to promote children's own aggression. *Journal of the American Academy of Child & Adolescent Psychiatry, 46*(8), 1080-1087.
Vik, T., Grote, V., Escribano, J., Socha, J., Verduci, E., Fritsch, M., & al., e. (2009). Infantile colic, prolonged crying and maternal postnatal depression. *Acta Paediatrica, 98*(8), 1344-1348.
Vitaro, F., Barker, E., Boivin, M., Brendgen, M., & Tremblay, R. E. (2006). Do early difficult temperament and harsh parenting differentially predict reactive and proactive aggression? *Journal of Abnormal Child Psychology, 34*(5), 685-695.
Volkow, N. D. (2004). The reality of comorbidity: depression and drug abuse. *Biological Psychiatry, 56*(10), 714-717.
Wadsworth, M. E., & Santiago, C. D. (2008). Risk and resiliency processes in ethnically diverse families in poverty. *Journal of Family Psychology, 22*(3), 399-410.
Wahlsten, D., & Gottlieb, L. N. (1997). The invalid separation of effects of nature and nurture: lessons from animal experimentation. In R. J. Stember & E. L. Grigorenko (Eds.), *Intelligence, heredity and environment*. Cambridge, UK: Cambridge University Press.
Wakschlag, L. S., & Hans, S. L. (1999). Relation of maternal responsiveness during infancy to the development of behavior problems in high-risk youths. *Developmental Psychology, 35*(2), 569-579.
Wald, M. S., Carlsmith, J. M., Leiderman, P. H., Smith, C., & French, R. d. (1988). *Protecting abused and neglected children*. Stanford, CA: Stanford University Press.
Waldron, M., Martin, N. G., & Heath, A. C. (2009). Parental alcoholism and offspring behavior problems: findings in Australian children of twins. *Twin Research and Human Genetics, 12*(5), 433-440.
Walton, A., & Flouri, E. (2010). Contextual risk, maternal parenting and adolescent externalizing behaviour problems: the role of emotion regulation. *Child: Care, Health and Development, 36*(2), 275-284.
Wareham, J. D., & Potenza, M. N. (2010). Pathological gambling and substance use disorders. *American Journal of Drug and Alcohol Abuse, 36*(5), 242-247.
Wathen, C. N., & MacMillan, H. L. (2003). Interventions for violence against women: scientific review. *JAMA: Journal of the American Medical Association, 289*(12578492), 589-600.
Weaver, I. C., Cervoni, N., Champagne, F. A., D'Alessio, A. C., Sharma, S., Seckl, J. R., . . . Meaney, M. J. (2004). Epigenetic programming by maternal behavior. *Nature Neuroscience, 7*(8), 847-854.
Weaver, I. C. G., Champagne, F. A., Brown, S. E., Dymov, S., Sharma, S., Meaney, M. J., & Szyf, M. (2005). Reversal of maternal programming of stress responses in adult offspring through methyl supplementation: altering epigenetic marking later in life. *Journal of Neuroscience, 25*(47), 11045-11054.
Webster-Stratton, C., Reid, M., & Stoolmiller, M. (2008). Preventing conduct problems and improving school readiness: evaluation of the Incredible Years teacher and child training programs in high-risk schools. *Journal of Child Psychology and Psychiatry and Allied Disciplines, 49*(5), 471-488.
Weder, N., Yang, B. Z., Douglas-Palumberi, H., Massey, J., Krystal, J. H., Gelernter, J., & Kaufman, J. (2009). MAOA genotype, maltreatment, and aggressive behavior: the changing impact of genotype at varying levels of trauma. *Biological Psychiatry, 65*(5), 417-424.
Weinstock, M. (2008). The long-term behavioural consequences of prenatal stress. *Neuroscience and Biobehavioral Reviews, 32*(6), 1073-1086.

Werner, E. E. (1997). Vulnerable but invincible: high-risk children from birth to adulthood. *Acta Paediatrica, 422*, 103-105.
Werner, E. E., & Smith, R. S. (1989). *Vulnerable but invincible: A longitudinal study of resilient children and youth*. New York, NY: Adams, Bannister, Cox.
Whitfield, C. L., Anda, R. F., Dube, S. R., & Felitti, V. J. (2003). Violent childhood experiences and the risk of intimate partner violence in adults - Assessment in a large health maintenance organization. *Journal of Interpersonal Violence, 18*(2), 166-185.
Widdowson, E. M., & McCance, R. A. (1963). The effect of finite periods of undernutrition at different ages on the composition and subsequent development of the rat. *Proceedings of the Royal Society of London. Series B: Biological Sciences, 158*, 329-342.
Widom, C. S. (1991). The role of placement experiences in mediating the criminal consequences of early childhood victimization. *American Journal of Orthopsychiatry, 61*(2048635), 195-209.
Widom, C. S., Raphael, K. G., & DuMont, K. A. (2004). The case for prospective longitudinal studies in child maltreatment research: commentary on Dube, Williamson, Thompson, Felitti, and Anda (2004). *Child Abuse and Neglect, 28*(7), 715-722.
Wiesner, M., Kim, H. K., & Capaldi, D. M. (2005). Developmental trajectories of offending: validation and prediction to young adult alcohol use, drug use, and depressive symptoms. *Development and Psychopathology, 17*(1), 251-270.
Wilcox, A. J. (2001). On the importance--and the unimportance--of birthweight. *International journal of epidemiology, 30*(6), 1233-1241.
Williams, E., & Radin, N. (1999). Effects of father participation in child rearing: twenty-year follow-up. *American Journal of Orthopsychiatry, 69*(3), 328-336.
Wind, T. W., & Silvern, L. (1994). Parenting and family stress as mediators of the longer-term effects of child abuse. *Child Abuse and Neglect, 18*(5), 439-453.
Winokur, M., Holtan, A., & Valentine, D. (2009). Kinship care for the safety, permanency, and well-being of children removed from the home for maltreatment. *Cochrane Database of Systematic Reviews*(19160287).
Wisenfeld, A., & Klorman, R. (1978). The mother's psychophysiological reactions to contrasting affective expressions by her own and an unfamiliar infant. *Developmental Psychology, 14*, 294-304.
Wolfe, D. A., Edwards, B., Manion, I., & Koverola, C. (1988). Early intervention for parents at risk of child abuse and neglect: a preliminary investigation. *Journal of Consulting and Clinical Psychology, 56*(3346447), 40-47.
Wolfe, D. A., Sandler, J., & Kaufman, K. (1981). A competency-based parent training program for child abusers. *Journal of Consulting and Clinical Psychology, 49*(7287972), 633-640.
World Health Organization. (2008). *Closing the gap in a generation: health equity through action on the social determinants of health: Final report of the Commission on Social Determinants of Health*. Geneva, Switzerland: WHO.
Worthman, C. M., & Kuzara, J. (2005). Life history and the early origins of health differentials. *American Journal of Human Biology, 17*(1), 95-112.
Wulczyn, F. (2004). Family reunification. *Future of Children, 14*(15072020), 94-9113.
Xie, R., He, G., Koszycki, D., Walker, M., & Wen, S. W. (2009). Fetal sex, social support, and postpartum depression. *Canadian Journal of Psychiatry, 54*(11), 750-756.
Yonas, M. A., Lewis, T., Hussey, J. M., Thompson, R., Newton, R., English, D., & Dubowitz, H. (2010). Perceptions of neighborhood collective efficacy moderate the impact of maltreatment on aggression. *Child Maltreatment, 15*(1), 37-47.
Zink, C. F., Tong, Y. X., Chen, Q., Bassett, D. S., Stein, J. L., & Meyer-Lindenberg, A. (2008). Know your place: Neural processing of social hierarchy in humans. *Neuron, 58*(2), 273-283.
Zwi, K., Woolfenden, S., Wheeler, D., O'Brien, T., Tait, P., & Williams, K. (2007). School-based education programmes for the prevention of child sexual abuse. *Cochrane Database of Systematic Reviews*(3).