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The effects of prenatal maternal stress on children's cognitive development: Project Ice Storm

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Abstract
There exists considerable research on the effects of prenatal maternal stress on offspring. Animal studies, using random assignment to experimental and control groups, demonstrate the noxious effects of prenatal maternal stress on physical, behavioural and cognitive development. The generalizability of these results to humans is problematic given that cognitive attributions moderate reactions to stressors. In humans, researchers have relied upon maternal anxiety or exposure to life events as proxies for the stressors used with animals. Yet, the associations between maternal anxiety or potentially non-independent life events and problems in infants are confounded by genetic transmission of temperament from mother to child. We summarize the literature on prenatal maternal stress and infant cognitive development, leading to the conclusion that the human literature lacks the ability to separate the effects of the objective exposure to a stressor and the mother's subjective reaction. We then describe our prospective *Project Ice Storm* in which we are following 150 children who were exposed *in utero* to a natural disaster. We demonstrate significant effects of the objective severity of exposure on cognitive and language development at age two years with important moderating effects of the timing during pregnancy. The implications of our findings are discussed.

Keywords: *Cortisol, foetal programming hypothesis, human, hypothalamo–pituitary–adrenal axis, language development, longitudinal study*

Introduction

Retrospective studies on humans, and experimental research with animals, suggest that psychosocial stressors during pregnancy can influence the physical, behavioural and cognitive outcomes of the offspring. There are important gaps in the existing literature, however.

Research on prenatal maternal stress is hampered by methodological constraints. Although animal studies are ideal in their control of prenatal and postnatal environments, the application of findings to humans is not always clear. Human studies, on the other hand, do not allow for stressful events to be randomly assigned during pregnancy by an experimenter and may be compromised by a host of potential confounds.

Natural and man-made disasters act as "natural experiments", randomising the distribution of stress exposure. The Québec Ice Storm of January 1998 qualifies as such an event. The storm resulted in electrical power failures for more than three million individuals for anywhere from 6 h to more than 5 weeks. As such, large numbers of pregnant women in various stages of pregnancy were randomly exposed to varying degrees of storm-related hardship.

The purpose of this paper is to review the existing literature on the effects of prenatal maternal stress, particularly with respect to infant cognitive development, and to present an introduction to our on-going longitudinal study of children exposed to the January 1998 Quebec Ice Storm while *in utero*. In addition, we will present early findings with respect to effects of

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the ice storm stress on children's cognitive and language development at age 2 years.

Effects of prenatal maternal stress (PNMS) on foetal and child development

There is a sizeable literature on the effects of prenatal maternal stress (PNMS) in rodents, non-human primates, and in humans. In humans, studies of prenatal maternal anxiety (Crandon 1979a, 1979b, Field et al. 1985, Grimm 1961) and of prenatal exposure to severe life events (Lou 1993) suggest that one of the first effects is on perinatal outcomes, with PNMS associated with a variety of severe obstetric complications, but especially with preterm birth (Paarlberg et al. 1999, 1995).

Weinstock reviewed the literature on prenatal stress, particularly rodent studies, and reports wide-ranging effects (Weinstock 2001). Rodent studies typically use various forms and intensities of restraint or noise to stress pregnant dams one to three times per day, usually for several days at some point between days 10 and 22 of gestation. Behavioural effects of prenatal exposure to various forms of stress are seen in social deficits and behaviours in rodent offspring suggestive of internalizing problems such as anxiety and depression. Controlled studies with non-human primates also indicate that PNMS results in behavioural alterations suggestive of internalizing problems (Clarke and Schneider 1993, Schneider 1992b).

Naturalistic studies with humans find similar effects on behaviour (Huizink et al. 2004). Studies of prenatal maternal anxiety (O'Connor et al. 2002, Van den Bergh and Marcoen, 2004), prenatal exposure to stressful life events (Stott 1973), and even prenatal exposure to dexamethasone (a synthetic glucocorticoid) (Trautman et al. 1995) are associated with children who are more withdrawn, anxious and depressed. A handful of retrospective studies have examined associations between independent stressors and mental health outcomes. A classic study by Huttunen and Niskanen (1978) examined rates of mental illness in samples from Finland in which the father had died either while the person was *in utero* or during the person's first year of life. Significantly greater rates of schizophrenia and other mental illness were found in the prenatal stress exposure group. Van Os and Selton (1998) also found a significant increase in rates of schizophrenia in Holland as a function of the German invasion during World War II. These studies show a specific effect of the timing of the stressor during the pregnancy, with the most noxious effects associated with exposure during the second trimester.

A number of other studies in non-human primates suggest that social stressors during gestation have negative effects on neurological functioning in the offspring, including reduced motor activity and maturity, less muscle tone and co-ordination, slower reaction time, and poorer balance (Schneider and Coe 1993, Schneider et al. 1999). In humans, significantly lower Prechtl neurological inventory scores 4–14 days after birth were found when mothers had experienced severe life events by mid-pregnancy (Lou et al. 1994).

PNMS studies have also discovered cognitive sequelae. In rodents, PNMS has resulted in impairment in maze learning (Nishio et al. 2001), reversal of learning set (Weller et al. 1988), and short and long-term memory (Gue 2004), while some studies show no effect on, for example, acquisition, discrimination or extinction in an operant conditioning task (Weller et al. 1988) or on object memory (Bowman 2004). Studies of non-human primates have found that both chronic stress during pregnancy (Schneider and Coe 1993, Schneider et al. 1999) and two-weeks of adrenocorticotrophic hormone administration at mid-gestation (Schneider 1992a) predict poorer attention, greater distractibility, and delayed object permanence (Schneider 1992a), an early indicator of cognitive development. Similar findings have been made in humans when linking mothers' self-reported stress levels (McIntosh et al. 1995) or anxiety (Van den Bergh and Marcoen 2004) during pregnancy to risk of attention-deficit and hyperactivity disorder (ADHD) in children. In a longitudinal study of anxiety in pregnant mothers and outcomes in their babies in England, O'Connor et al. showed that, even after controlling for a host of potential confounding factors, higher levels of anxiety experienced by the mother at weeks 12–22 of pregnancy significantly predicted more severe attention problems in the children at 18 and 32 months of age (O'Connor et al. 2002). Another study found that at 9 years of age, children of women who were highly anxious during pregnancy showed more attention deficits than children of low anxiety women (Mulder et al. 2002). Chronic stress resulting from moderate daily hassles (Stott 1973) and state and/or trait anxiety (Brouwers et al. 2001) are also associated with delayed language development and lowered intellectual functioning, respectively.

The effects of PNMS on cognitive development may be due to an effect on foetal brain development. PNMS in rodents predicts the degeneration of hippocampal neurons (Uno et al. 1989, 1990) and reductions in the size of the hippocampus by as much as 30% (Uno et al. 1994), which might be manifest in reduced memory functioning. Lower scores on cognitive tests may be due, in part, to the indirect effects of prenatal stress on attentional functioning.

Timing of teratogens

It has been hypothesised that it may be less the *type* of disruption of foetal neural development than the *timing* that is critical in determining risk for negative

outcomes since the timing of an insult may indicate which developmental processes are likely to be affected (Mednick et al. 1988). A common theme among many studies of PNMS is that the worst outcomes are associated with stressors timed at mid-gestation (Glynn et al. 2001, Huizink et al. 2004, Huttenen and Niskanen 1978, O'Connor et al. 2002, 2003, Schneider et al. 1992, Watson et al. 1999), a critical period for brain development (Andreason 1999, Weinberger 1995). Moreover, if outcomes are mediated through foetal hypothalamus–pituitary–adrenal (HPA) axis activity, its influence should only be seen in mid-gestation after the foetal HPA axis becomes functional (Gitau et al. 2001). Furthermore, reports suggest that mothers may become more immune to the potential negative effects of stress as their pregnancy advances into the 3rd trimester of pregnancy (Glynn et al. 2001, Kammerer et al. 2002). However, some researchers have found effects of 3rd trimester stress on obstetric complications (Crandon 1979b). Also, it has been reported that early gestation stress in non-human primates has a more detrimental effect on birth weight and neuromotor functioning than mid-late gestational stress (Schneider et al. 1999). Thus, the question of timing of prenatal stress is intimately associated with the outcome factor of interest.

Critique of the literature

There is no shortage of studies of prenatal maternal stress. Yet, to date, there have been no ideal studies of PNMS that can determine the extent, longevity and mechanisms of the effects in humans. In animal research, "subjects" can be randomly assigned to various stress conditions. While these studies can provide working hypotheses on the mechanisms by which PNMS influences outcomes, there are limitations to animal studies. First, rats are not born at the same stage of development as humans are. Secondly, rat and primate studies are unable to take into account the kinds of cognitive appraisals that occur in humans between an external stressor and the response to the stressor which may well be the critical variable in determining a pregnant woman's physiological response to a stressor (Lazarus 1991) and subsequent damage to the foetus.

The human studies that do assess "stress" during the pregnancy are also unable to tease apart the various aspects of the process. Studies of anxiety during pregnancy cannot separate state versus trait anxiety, the latter of which may be passed on to babies, in part, genetically (Rowe 1994) and through parenting style and modelling, as well as through the complicated mechanisms of gene-by-environment correlations (Rutter and Silberg 2002). Studies of life events during pregnancy are equally hampered in that such events are far from being randomly assigned to women; divorce and job loss are not always "independent" life events but may, instead, be influenced by heritable personality traits. Most human studies of stress also have limited statistical power: An extremely large sample of pregnant women is required to include a sufficient number who had experienced an independent life event. And the large-scale retrospective studies of independent life events (death of father, hurricane, tornado, foreign invasion) are too far removed from the incident to assess the pregnant woman's appraisal of the event. What is needed to permit us to tease apart the objective and the subjective components of the stress process is a man-made or natural disaster that affects large numbers of pregnant women in a quasi-random fashion.

Disaster research

Disasters provide unique opportunities to study the effects of stress in people. Disasters are characterised by "disruption exceeding the adjustment capacity of the affected community" (Lechat 1979, p. 11) and range from oil spills to hurricanes and earthquakes. Important dimensions of disasters include loss (of persons or property), threat to life or physical integrity, scope and duration, blame for the event (man versus nature), familiarity with similar events, speed of onset and amount of displacement or change. Since events differ along many dimensions, one must tailor-make disaster questionnaires in order to assess degree of exposure.

Standardised instruments, however, have proven useful in estimating the psychological impact of disasters. One review of 52 studies concluded that, on average, sudden onset disasters are associated with a 17% increase in the prevalence of psychological disorders (Rubonis and Bickman 1991) including post-traumatic stress disorder (Palinkas et al. 1993). When response is measured along a psychopathology continuum, disasters have been shown to be associated with significant increases in psychological symptoms. One review uncovered 7 so-called "natural experiments" in which a disaster struck a community that had recently been surveyed in an epidemiological study, providing estimates of pre- and post-disaster symptoms on the same subjects. These studies confirm the disaster effect (Bromet and Dew 1995). In some instances, the emotional effects of a disaster may last for many years as shown in a recent 11-year follow-up of women evacuated to Kyev following the Chernobyl nuclear power plant explosion (Adams et al. 2002).

Questions remaining about prenatal maternal stress

The available literature on prenatal maternal stress suggests that a large gap exists: Understanding how the various elements of the stress process

(in particular, the objective exposure versus the subjective reaction) operate, individually and in combination, to influence cognitive and other outcomes in the unborn human child. In order to successfully disentangle the objective elements of the stress process from the mother's own temperament (which can be passed on to her children through a combination of genetics, the prenatal environment, and parenting style, not to mention the influence of the mother's own temperament on her response style as she completes questionnaires rating her child) one requires an independent stressor that affects large numbers of pregnant women and which is distributed in a relatively random fashion.

Project Ice Storm

Project Ice Storm was initiated soon after a series of freezing rain storms hit Southern Quebec in Canada between January 5 and 9, 1998. The build-up of ice on utility lines toppled more than 1000 electrical pylons and more than 25,000 wooden transmission poles resulting in electrical power failures during the dead of winter for more than 1.4 million households in more than 700 municipalities. More than three million individuals experienced power outages ranging from a few hours to more than 6 weeks. Four hundred and fifty emergency shelters were established which slept as many as 17,000 people in a single night. In Quebec, at least 27 people died as a result of hypothermia, accidents, or carbon monoxide poisoning or fire associated with unconventional heating methods. Thousands of people were injured or hospitalized as a result of the storm. The agricultural sector suffered major financial losses associated with the power outage: Thousands of animals were lost when ventilation and heating systems or milking machinery could not be kept going. The maple syrup industry was nearly obliterated due to the near total loss of branches on maple trees. There were $1 Billion worth of insurance claims, $3 Billion of lost income to businesses and $1 Billion dollars required to repair hydroelectric infrastructure. More than 46,000 people were laid off work as a direct or indirect consequence of the crisis. Everyone had to deal with 5-inch ice build-up on cars, streets, trees and roofs. Several buildings collapsed under the weight of ice and snow and more than 200 people were hospitalized with severe injuries as a result of falling off their roofs while removing snow and ice; 3 people died in this way. (Statistics provided by *Ministère de la Sécurité Publique*.)

Thus, the 1998 Quebec ice storm provided a unique opportunity. The objective of *Project Ice Storm* is to determine the nature and duration of the effects of an independent stressor during pregnancy on the unborn child in a prospective design with a relatively large sample of families. By conducting repeated assessments of women affected by the ice storm, as well of their children, over several years, we are determining the effects of objective stress exposure and subjective stress reaction on perinatal outcomes, maternal postpartum depression, and the behavioural, physical and cognitive development of the children.

Method

Sample development

The area of Québec that was worst hit by the storm was the region called the Montérégie, an area southeast of Montreal that is mainly suburban and rural and which came to be known as "the Black Triangle". To identify potential subjects, we contacted the four hospitals in the region and obtained the names of physicians authorized to deliver babies there. Approximately 20 doctors identified more than 1400 women who met our inclusion criteria: They were pregnant on January 9, 1998 or became pregnant during the 3 months following the storm, were 18 years of age or older, and spoke fluent French.

On June 1, 1998, we delivered the appropriate number of pre-stamped questionnaires to each participating clinic where clinic staff addressed the envelopes and mailed them. Of the 1440 questionnaires sent out, 224 were returned for a response rate of 15.5% which is considered to be the norm for unsolicited postal questionnaires. This response rate may be explained also by the fact that during the summer of 1998 the potential subjects were either pregnant or caring for a newborn, as well as for any older children, and may also have been dealing with ice storm-related damage to the home and financial sequelae. Of the 224 women who responded to the first questionnaire, 178 provided their name and address and agreed to further contact. We have continued to follow as many of these families as possible; many have not been followed since because their ice storm pregnancy ended in miscarriage or stillbirth, while others have been lost to follow-up, and a small number have refused continued involvement, leaving 141 families who are continuing their participation in the study.

Instruments

In total, we have made contact with the families 7 times between June 1998 and the children's 6th birthday with an eighth contact on-going and a ninth in the planning stage for an evaluation at age $7\frac{1}{2}$ years.

Questionnaire #1—Reactions to the Storm, was sent on June 1, 1998. The primary goal of the first questionnaire was to evaluate the extent of the women's objective exposure to the ice storm, as well as their subjective reaction to the storm. In order to assess objective exposure, we examined the literature on natural disasters. We formulated questions (Table I)

Table I. Questions used to assess the four dimensions (Threat, Loss, Scope, and Change) of our objective stress questionnaire that the mothers completed shortly after the ice storm.

Threat	Loss	Scope	Change
1. Were you injured?	1. Did your residence suffer damage as a result of the ice storm?	1. How many days were you without electricity?	1. Did your family stay together for the duration of the ice storm?
2. Was anyone close to you injured?	2. Did you experience a loss of personal income?	2. How many days were you without the use of your telephone?	2. Did you spend any time in a temporary shelter?
3. Were you ever in danger due to:	3. Did you suffer a loss of business income?		3. How often were you required to change residence during the ice storm?
3.1. …the cold			4. Did you take in guests during the ice storm?
3.2. …exposure to downed electrical power lines			5. Did you experience an increase in physical work during the ice storm?
3.3. …exposure to carbon monoxide			
3.4. …lack of potable water			
3.5. …lack of food			
3.6. …falling branches & ice			

that would reflect the participant's experiences related to 4 categories of exposure used in other disaster studies: Threat, Loss, Scope and Change (Bromet and Dew 1995). Each dimension was scored on a scale of 0–8, ranging from no exposure to high exposure. A total objective stress score was calculated by summing scores from all four dimensions using McFarlane's approach (McFarlane 1988). Because there was no theoretical basis to believe that any one of the four dimensions of our scale was more distressing than the other dimensions, and based on McFarlane's study of Australian fire fighters (McFarlane 1988), each dimension was weighted equally to obtain the total score of our scale which we dubbed STORM32.

Questionnaire #1 also included an assessment of the women's subjective stress reaction to the ice storm. In the literature on natural disasters and trauma, one instrument stands out as being the gold-standard measurement of subjective reactions: The Impact of Event Scale–Revised (Weiss and Marmar 1997). The 22-item scale describes symptoms from three categories relevant to post-traumatic stress disorder: Intrusive thoughts, hyperarousal and avoidance. A French-version of the scale was developed and validated by our team (Brunet et al. 2003) to reflect the mothers' symptoms relative to the ice storm crisis. Participants respond on a 5-point Likert scale, from *Not at all* to *Extremely*, the extent to which the behaviour describes how they felt over the preceding seven days.

To assess the severity of maternal psychiatric and stress-related symptoms in general, we have used, at various times, either the General Health Questionnaire (Goldberg 1972) which includes scales reflecting anxiety, depression, somatic symptoms and dysfunction, or the Edinburgh Postnatal Depression Scale (Cox et al. 1987). Mothers have also indicated, since the birth of their baby, their experiences with any other life events in the preceding 12 months using a modified version of the Life Experiences Survey (Sarason et al. 1978). We have also assessed the mothers' personality using the short form (60-item) NEO Five Factor Inventory (Costa and McCrae 1992) which includes scales for neuroticism, extroversion, openness to experience, agreeableness and conscientiousness. Using data on maternal and paternal education and occupation, we estimated socioeconomic status using the Hollingshead scale (Hollingshead 1973).

Laboratory assessment. When the children were 2 years old, a subset of 61 families participated in a laboratory assessment of cognitive (Bayley Scales of Infant Development, 2nd Edition Bayley 1993), language (MacArthur Communicative Development Inventory (Fenson et al. 1993)) and functional play (Zelazo and Kearsley 1980) development. These families were selected to represent the lowest and highest thirds in severity of objective ice storm stress, and the 3 trimesters of exposure. Children with severe low birth weight, Caesarian-section delivery, or prenatal smoking or other severe prenatal stressor (e.g. death of close relative) were excluded.

Results: The ice storm and cognitive development

Here, we provide an overview of findings on the effects of prenatal exposure to the ice storm on cognitive development at age two years. These results have been

published (Laplante et al. 2004), or are under review (Laplante et al. submitted), elsewhere.

Reaction to the storm

The mothers in our sample spent, on average, 14.9 (SD = 8.9) days without electricity and 4.4 (SD = 8.4) days without the use of their telephone. Approximately 65% of the mothers spent at least one night away from their home for a period, on average, of 9.2 (SD = 11.2) nights away from their home, changing locations, on average, 1.3 (SD = 1.2) times. Of the mothers who remained in their homes during the ice storm, 37.7% had guests staying with them: On average, 1.4 (SD = 2.4) guests stayed for an average of 30 days (SD = 5.9). Approximately half of the mothers reported damage to their homes (46.6%) and loss of personal income (44.7%) directly related to the ice storm. Six percent of the mothers were physically injured as a result of the ice storm and 37.7% reported being worried about the personal safety of loved ones.

Based on the items included in the four 8-point scales of our STORM32 objective stress measure, the mothers in our sample scored, on average, 3.0 points (SD = 2.6) on our Scope dimension, 3.0 points (SD = 1.9) on our Loss dimension, 3.1 points (SD = 1.7) on our Change dimension, and 1.5 points (SD = 1.4) on our Threat dimension. Overall, the mothers in our sample scored, on average, 10.4 points (SD = 4.9) on our total STORM32 scale.

In terms of subjective stress reaction, the mothers in our sample scored, on average, 11.9 points (SD = 12.5) on our French-version of the IES-R scale. Using the cut-off of 22 points on this scale, 16.6% of the mothers exhibited levels of subjective stress reaction that placed them within the clinical range for potential post-traumatic stress disorder.

Intellectual, language and play abilities at 2 years

To examine interactions between trimester of exposure and severity of ice storm stress, we split STORM32 into three groups (low, moderate and high stress), and contrasted the low stress group with the combined moderate-high stress group. We found that moderate-high objective prenatal maternal stress was associated with poorer intellectual and language functioning at the age of two years (Laplante et al. 2004). These findings were reinforced by the results of our analyses of the children's play behaviours (Laplante et al. submitted). For intellectual abilities, children whose mothers were exposed to the ice storm during their 1st or 2nd trimester of pregnancy and who experienced moderate or high objective stress had significantly lower Bayley MDI scores. For the 1st trimester exposed children, the moderate-high stress group had an average score 14 points lower (i.e. 0.95 of 1 SD) than their counterparts in the low stress group (see Figure 1). For the 2nd trimester exposed group, children from the moderate-high stress group scored an average of 19.5 points lower than their counterparts in the low stress group, a 1.3 SD difference. These effects remained even after controlling for age at testing, birth weight, subjective stress scores (IES-R), and socioeconomic status, with an adjusted overall difference of 9.5 points between stress groups across all three trimesters. There were no effects of stress severity on the MDI scores for children exposed in the third trimester of pregnancy.

Using maternal reports of their children's word comprehension and word use at age 2 years, we found

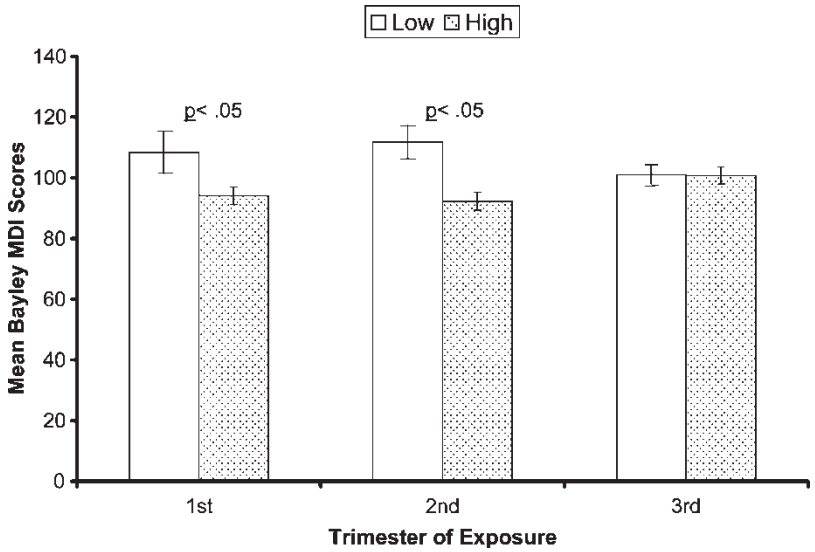

Figure 1. Toddlers' mean (± standard error) Bayley mental development idex (MDI) scores at 2 years of age, as a function of objective prenatal maternal stress levels (low, high) and trimester of exposure (1st, 2nd, or 3rd).

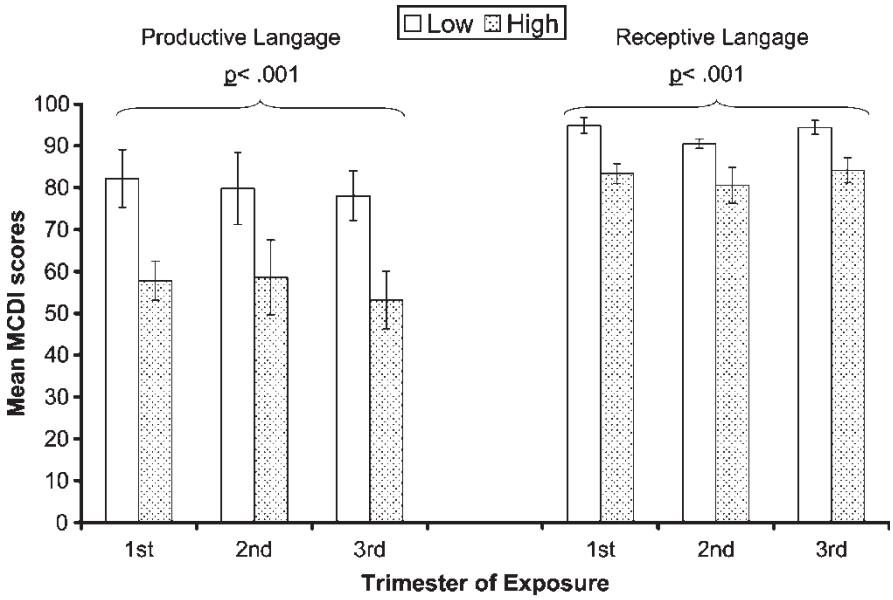

Figure 2. Toddlers' mean (± standard error) MacArthur communicative development index (MCDI) scores for productive and receptive language abilities at 2 years of age, as a function objective prenatal maternal stress levels (low, high) and trimester of exposure (1st, 2nd, or 3rd).

similar effects of objective stress severity, but without the differential effect of trimester of exposure (Figure 2). Children whose mothers were exposed to moderate-high objective stress spoke, on average, 20.2 fewer words ($p < 0.001$) which represents a 30% reduction in productive vocabulary. There was also a significant effect of objective ice storm exposure on receptive vocabulary, again with no differential effect by timing of exposure. At age 2 years, children of mothers from the moderate-high objective stress group understood, but did not yet speak, an average of 10.5 fewer words ($p < 0.001$) than their low stress counterparts, representing 11% fewer words.

Because a two year-old's performance on structured tasks may reflect temperamental or behavioural characteristics rather than purely cognitive skills, we included a non-structured free-play task that was videotaped and rated blind to prenatal stress level. Toy play during early childhood evolves in a predictable manner and provides excellent discriminative and predictive validity as a measure of cognitive function. The youngest toddlers will engage in "stereotypical" play which involves banging, waving or mouthing toys. Older toddlers will engage in "relational" play by touching two toys together in a non-functional manner. A more mature level of toy play involves using objects according to their intended function. Thus, in "functional" toy play, a child may roll a car on the floor while making car noises, or pour imaginary tea from a pot into a teacup. The results of this study support the findings from the Bayley Scales with moderate-high stress children engaging in significantly more stereotypical play and less functional play than their low stress counterparts, and with the effects limited to children exposed during the 1st and 2nd trimesters ($p < 0.01$; Figure 3). For 2nd trimester children, the level of objective maternal stress (STORM32 score) accounted for 53.8% of the variance in the level of the children's functional toy play, while the mother's subjective stress (IES-R) explained an additional 13.6% of the variance, even after controlling for the children's birth weights, the number of obstetric complications experienced by the mothers and the mothers' level of anxiety during pregnancy ($p < 0.005$). Maternal objective and subjective PNMS was not related to the functional play levels of children exposed during the 1st or 3rd trimester of pregnancy.

We have conducted additional cognitive assessments of the children at age $5\frac{1}{2}$ years. Preliminary examination of the data suggests that the effects of objective prenatal maternal stress on cognitive and language development persist into middle childhood (unpublished data). A repeat assessment is planned for age $7\frac{1}{2}$ during 2005–2006.

Discussion

The findings from *Project Ice Storm* strongly suggest that a major stressful event, independent of maternal personality factors, can have a negative impact on cognitive and language development of the unborn child. Other results not reported here also demonstrate significant noxious effects of the severity and/or timing of prenatal maternal stress on perinatal outcomes, infant temperament, behavioural and emotional functioning, and even physical development of children exposed *in utero*. We have uncovered several effects that are related to the timing of the stressor, with a particular emphasis on the 2nd trimester.

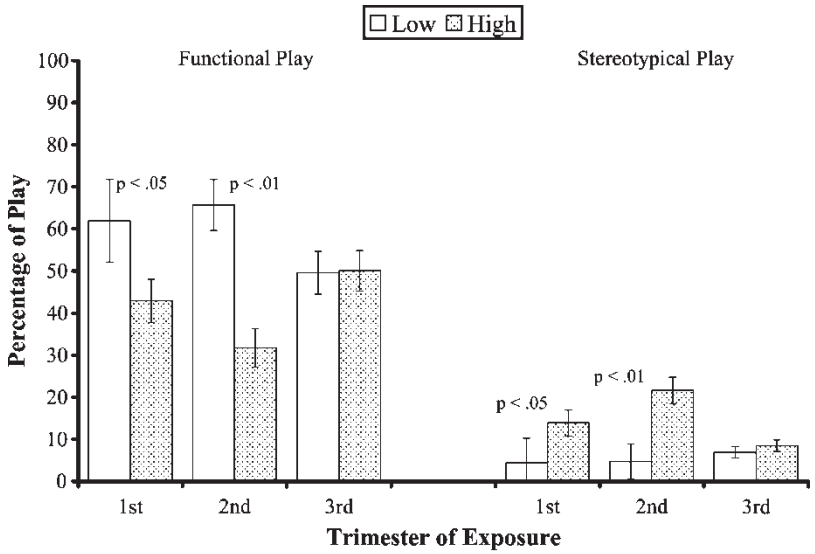

Figure 3. Percentage of functional and stereotypical play exhibited by the toddlers as a function of level of maternal objective stress (high or low) and trimester of exposure.

Furthermore, while there have been a handful of results implicating the mother's subjective reaction to the stressor, the majority of findings implicate the degree of her objective exposure to the event.

The mechanism by which prenatal maternal stress affects the pregnancy and the subsequent development of the children, however, remains unknown for human populations, although maternal glucocorticoids are often cited as a likely teratogen. There is much support for the role of maternal glucocorticoids in the PNMS effect in animals (Weinstock 2001, Schneider et al. 1992). In humans, indirect evidence for effects of maternal hormones is available. Trautman et al. (1995) conducted a study of children whose mothers had received dexamethasone (DEX) (a synthetic glucocorticoid) during pregnancy for congenital adrenal hyperplasia (CAH). They found that these children were significantly more withdrawn and emotional and significantly less social at one year of age, and had significantly higher scores on a scale of internalising problems at ages 2–3 years than a group of comparison children whose CAH mothers went untreated with DEX. These data suggest that it is maternal stress hormones that are responsible for the effects seen in children.

Although we have shown, in *Project Ice Storm*, that objective PNMS in early gestation predicts poorer cognitive functioning, we have not so far been able to show that these findings are the direct effects of the stress exposure either on maternal cortisol levels or on disruptions in foetal brain development. Although we obtained salivary cortisol samples from the mothers in our study at the time of our first contact, those samples were taken five-to-six months after the storm, when half of the mothers had given birth, rendering our maternal cortisol data difficult to interpret.

There are also animal studies showing that PNMS is associated with alterations in stress reactivity in the offspring which may be involved in a variety of cognitive and behavioural outcomes. In rhesus monkeys, for example, prenatal exposure to either glucocorticoids or to stress is associated with greater increases in cortisol following a stressor (Uno et al. 1994). These offspring also show a slower recovery following stress (Uno et al. 1994). Greater stress reactivity is also found in prenatally stressed rats (Koehl et al. 1999, Takahashi and Kalin 1991, Weinstock et al. 1992), whose stress-induced corticosterone secretion is also prolonged, that is, their recovery from the stressor is slower (Fride et al. 1986, Maccari et al. 1995). We are currently analyzing data related to the children's hormonal stress responsivity which may support an effect of PNMS on the development of the foetal HPA axis. A subset of children provided saliva samples before and after their pre-kindergarten inoculation session. Their cortisol data will be analyzed to determine effects of PNMS, and to determine moderating effects of the trimester of exposure and the child's sex.

There are other potential mechanisms for the effect of PNMS that *Project Ice Storm* is unable to investigate. Although a stress- or disaster-related reduction in supply of nutrients to the mother and foetus may be involved in the process, we failed to include questions about eating patterns in our initial ice storm questionnaire. Maternal thyroid function may have compromised as a result of the cold, but this, too, went unmeasured. There was a great deal of water damage to homes as a result of ice build-up on roofs which fostered the production of moulds in many homes and could, potentially, have had an effect on the pregnant women. Yet this type of damage, as well, was not

addressed in our survey. Finally, a compromised gas exchange across the placenta may have been involved in the stress effect seen in our sample, but these data are not available in the majority of hospital records. For a random subsample of cases, however, placental weight at birth is available from hospital charts, and we are currently investigating associations between stress levels and placental weight on one hand, and between placental weight and developmental outcomes on the other.

Although we are lacking data on the immediate biological processes that may have mediated between stress exposure or stress reaction in the mother and developmental processes in the foetus, we are in a position to determine whether the effects of PNMS exposure on cognitive outcomes are due to permanent insults to brain development by obtaining structural magnetic-resonance images (MRI) of the children, a project currently in development. Research suggests that either stress or administration of stress hormones to pregnant females results in severe degenerative changes in neurons within the hippocampus (Uno et al. 1990), resulting in an overall reduction in hippocampal volume, even though the total brain volume remains unchanged (Uno et al. 1994) in these animals. In addition, magnetic resonance imaging studies indicate that this hippocampal volume loss is maintained 2-years postnatally (Uno et al. 1994). Using an acoustic startle protocol with rhesus monkeys, Coe and colleagues (Coe et al. 2003, Coe et al. 2002) report similar findings to those obtained by Uno. Both early (days 50–92) and late (days 105–147) stress to pregnant non-human primate females result in a reduction in the size (Coe et al. 2003) and alterations to the shape (Coe et al. 2002) of the hippocampus. To date, no study has used a prospective design to examine the potential impact of prenatal maternal stress on the structural development of the hippocampus in humans. Thus, our MRI scans of ice storm children will target hippocampal volumes as well as other regions.

Weather researchers agree that the visible effects of global warming will be more frequent and more severe extreme weather events. Moreover, man-made threats, such as terrorist attacks on civilian populations, are becoming more prevalent. Such events will lead to greater numbers of pregnant women facing stressful events that are outside of their control and that will result in foetuses experiencing increasing levels of prenatal maternal stress. Therefore, research is required to better understand the process by which prenatal maternal stress influences prenatal development and postnatal outcomes.

We propose that a first step in understanding these mechanisms is to separate the stressful event into its components, such as objective levels of exposure to hardship, and subjective emotional reactions to that hardship. Evaluation of objective stress involves examining the specific events faced by the pregnant women during the crisis, such as duration of power loss, loss of income and amount of change to the physical environment. The second component, subjective reaction to the objective stress, involves assessing the pregnant women's psychological response to these specific events. Borrowing from the literature on post-traumatic stress disorder, these subjective responses will include varying degrees of hyperarousal, avoidance of the traumatic event, and intrusive thoughts about the event. Separation of the objective and subjective aspects of a person's stressful experience is important in that it will enable researchers to make recommendations on how to prevent, or limit, the potential negative effects of prenatal stress on the developing foetus. For example, if it is found that particular aspects of the objective exposure (such as amount of change, or physical exertion) carry the greatest weight in the teratogenic effects, then public health and safety personnel may need to ensure that pregnant women exposed to a natural disaster are sent immediately to very safe areas rather than being moved several times. If, however, it is found that the greatest harm to the foetus results from the mother's physiological hyperarousal following a disaster, then psychological (e.g. biofeedback) or pharmacological interventions may be warranted to limit damage to the foetus. Thus, projects such as *Project Ice Storm* will assist in, first, identifying the most vulnerable subgroups of pregnant women and, secondly, lead to recommendations targeted at limiting damage.

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References

Adams RE, Bromet EJ, Panina N, Golovakha E, Goldgaber D, Gluzman S. 2002. Stress and well-being in mothers of young children 11 years after the Chernobyl nucelar power plant accident. Psychol Med 32:143–156.

Andreason NC. 1999. A unitary model of Schizophrenia: Bleuler's "fragmented phrene" as schizencephaly. Arch Gen Psychiatry 56:781–787.

Bayley N. 1993. Bayley scales of infant development. 2nd ed., San Antonio: Psychological Corporation.

Bowman. 2004. Sexually dimorphic effects of prenatal stress on cognition, hormonal responses, and central neurotransmitters. Endocrinology 145:3778–3787.

Bromet E, Dew MA. 1995. Review of psychiatric epidemiologic research on disasters. Epidemiol Rev 17(1):113–119.

Brouwers EPM, van Baar EL, Pop VJM. 2001. Maternal anxiety during pregnancy and subsequent infant development. Infant Behav Dev 24:95–106.

Brunet A, St-Hilaire A, King S. 2003. Validation of a French version of the impact of event scale—revised. Can J Psychiatry 48: 55–60.

Clarke AS, Schneider ML. 1993. Prenatal stress has long-term effects on behavioral responses to stress in juvenile rhesus monkeys. Dev Psychobiol 26:293–304.

Coe CL, Lulbach GR, Schneider ML. 2002. Prenatal stress alters the size and shape of the corpus callosum in the infant monkey. Dev Psychobiol 41:178–185.

Coe CL, Kramer M, Czéh B, Gould E, Reeves AJ, Kirschbaum C, et al. 2003. Prenatal stress diminishes neurogenesis in the dentate gyrus of juvenile rhesus monkeys. Biol Psychiatry 54:1025–1034.

Costa JF, McCrae RR. 1992. Revised NEO personality inventory (NEO-PI) and NEO five-factor inventory (NEO-FFI) professional manual. Odessa, FL: Psychological Assessment Resources.

Cox JL, Holden JM, Sagovsky R. 1987. Detection of postnatal depression: Development of the 10-item Edinburgh postnatal depression scale. Br J Psychiatr 150:782–786.

Crandon AJ. 1979a. Maternal anxiety and neonatal wellbeing. J Psychosom Res 23:113–115.

Crandon AJ. 1979b. Maternal anxiety and obstetric complications. J Psychosom Res 23:109–111.

Fenson L, Dale P, Reznick J. 1993. MacArthur communicative development inventories: User's guide and technical manual. San Diego: Singular Publishing Group.

Field T, Sandberg D, Quetel TA, Garcia R, Rosario M. 1985. Effects of ultrasound feedback on pregnancy anxiety, fetal activity, and neonatal outcome. Obstet Gynecol 66:525–528.

Fride E, Dan Y, Feldon J, Halevy G, Weinstock M. 1986. Efects of prenatal stress on vulnerability to stress in prepubertal and adult rats. Physiol Behav 37:681–687.

Gitau R, Fisk NM, Teixeira JMA, Cameron A, Glover V. 2001. Fetal hypothalamic–pituitary–adrenal stress responses to invasive procedures are independent of maternal responses. J Clin Endocrinol Metab 86:104–109.

Glynn LM, Wadhwa PD, Dunkel Schetter C, Chicz-Demet A, Sandman CA. 2001. When stress happens matters: Effects of earthquake timing on stress responsivity in pregnancy. Am J Obstet Gynecol 184:637–642.

Goldberg DP. 1972. The detection of psychiatric illness by questionnaire: A technique for the identification and assessment of non-psychiatric illness. London: Oxford University Press.

Grimm EG. 1961. Psychological tension in pregnancy. Psychosom Med 23:520–527.

Gue. 2004. Sex differences in learning deficits induced by prenatal stress in juvenile rats. Behav Brain Res 150:149–157.

Hollingshead AB. 1973. Four-factor index of social status. New Haven: Yale University Press.

Huizink AC, Mulder EJH, Buitelaar JK. 2004. Prenatal stress and risk for psychopathology: Specific effects or induction of general susceptibility? Psychol Bull 130:115–142.

Huttenen MO, Niskanen P. 1978. Prenatal loss of father and psychiatric disorders. Arch Gen Psychiatry 35:429–431.

Kammerer M, Adams D, von Castelberg B, Glovert V. 2002. Pregnant women become insensitive to cold stress. BMC Pregnancy and Childbirth 2:8.

Koehl M, Darnaudery M, Dulluc J, Van Reeth O, Le Mooal M, Maccari S. 1999. Prenatal stress alters circadian activity of hypothalamic–pituitary–adrenal axis and hippocampal corticosteroid receptors in adult rats of both genders. J Neurobiol 40:302–315.

Laplante DP, Barr RG, Brunet A, Galbaud du Fort G, Meaney M, Saucier J-F, et al. 2004. Stress during pregnancy affects intellectual and linguistic functioning in human toddlers. Pediatr Res 56:400–410.

Laplante DP, Zelazo PR, Brunet A, King S. (submitted). Functional play at 2 years of age: Effects of prenatal maternal stress. J Am Acad Child Adolesc Psychiatry.

Lazarus RS. 1991. Emotion and adaptation. New York: Oxford University Press.

Lechat MF. 1979. Disasters and public health. Bull World Health Organ 57:11–17.

Lou HC. 1993. Prenatal stressful events of human life affect fetal brain development. Neuropediatrics 24(Abstract):180.

Lou HC, Hansen D, Nordentoft M, Pryds O, Jensen F, Nim J, et al. 1994. Prenatal stressors of human life affect brain development. Dev Med Child Neurol 36:826–832.

Maccari S, Piazza PV, Kabbaj M, Barbazanges A, Simon H, Le Moal M. 1995. Adoption reverses the long-term impairment in glucocorticoid feedback induced by prenatal stress. J Neurosci 15:110–116.

McFarlane AC. 1988. Relationship between psychiatric impairment and a natural disaster: The role of distress. Psychol Med 18(1):129–139.

McIntosh DE, Mulkins RS, Dean RS. 1995. Utilization of maternal perinatal risk indicators in the differential diagnosis of ADHD and UADD children. Int J Neurosci 81:35–46.

Mednick SA, Machon RA, Huttunen MO, Bonett D. 1988. Adult schizophrenia following prenatal exposure to an influenza epidemic. Arch Gen Psychiatry 45:189–192.

Mulder EJH, Robles de Medina PG, Huizink AC, Van den Bergh BRH, Buitelaar JK, Visser GHA. 2002. Prenatal maternal stress: Effects on pregnancy and the (unborn) child. Early Hum Dev 70:3–14.

Nishio H, Kasuga S, Ushijima M, Harada Y. 2001. Prenatal stress and postnatal development of neonatal rats—sex-dependent effects on emotional behavior and learning ability of neonatal rats. Int J Dev Neurosci 19(1):37–45.

O'Connor TG, Heron J, Golding J, Beveridge M, Glover V. 2002. Maternal antenatal anxiety and children's behavioural/emotional problems at 4 years. Br J Psychiatry 180: 502–508.

O'Connor TG, Heron J, Golding J, Glover V, Team AS. 2003. Maternal antenatal anxiety and behavioural/emtional problems in children: A test of a programming hypothesis. J Child Psychol Psychiatry 44:1025–1036.

Paarlberg KM, Vingerhoets AJ, Passchier J, Dekker GA, Van Geijn HP. 1995. Psychosocial factors and pregnancy outcome: A review with emphasis on methodological issues. J Psychosom Res 39(5):563–595.

Paarlberg KM, Vingerhoets AJ, Passchier J, Dekker GA, Heinen AG, van Geijn HP. 1999. Psychosocial predictors of low birthweight: A prospective study. Br J Obstet Gynaecol 106(8):834–841.

Palinkas LA, Petterson JS, Russell J, Downs MA. 1993. Community patterns of psychiatric disorders after the Exxon Valdez oil spill. Am J Psychiatry 150:1517–1523.

Rowe DC. 1994. The limits of family influence: Genes, experience, and behavior. New York: Guilford.

Rubonis AV, Bickman L. 1991. Psychological impairment in the wake of disaster: The disaster-psychopathology relationship. Psychol Bull 109:384–399.

Rutter M, Silberg J. 2002. Gene-environment interplay in relation to emotional and behavioral disturbance. Annu Rev Psychol 53:463–490.

Sarason IG, Johnson JH, Siegel JM. 1978. Assessing the impact of life changes: Development of the life experience survey. J Consult Clin Psychol 46(5):932–946.

Schneider ML. 1992a. Delayed object permanence development in prenatally stressed rhesus monkey infants (*Macaca mulatta*). Occup Ther J Res 12(2):96–110.

Schneider ML. 1992b. Prenatal stress exposure alters postnatal behavioral expression under conditions of novelty challenge in rhesus monkeys. Dev Psychobiol 25:529–540.

Schneider ML, Coe CL. 1993. Repeated social stress during pregnancy impairs neuromotor development in the primate infant. J Dev Behav Pediatr 14(2):81–87.

Schneider ML, Coe CL, Lubach GR. 1992. Endocrine activation mimics the adverse effects of prenatal stress on the neuromotor development of the infant primate. Dev Psychobiol 15:427–439.

Schneider ML, Roughton EC, Koehler AJ, Lubach GR. 1999. Growth and development following prenatal stress exposure in primates: An examination of ontogenetic vulnerability. Child Dev 70:263–274.

Stott DH. 1973. Follow-up study from birth of the effects of prenatal stresses. Dev Med Child Neurol 15:770–787.

Takahashi LK, Kalin NH. 1991. Early developmental and temporal characteristics of stress-induced secretion of pituitary–adrenal hormones in prenatally stressed rat pups. Brain Res 558:75–78.

Trautman PD, Meyer-Bahlburg HFL, Postelnek J, New MI. 1995. Effects of early prenatal dexamethasone on the cognitive and behavioral development of young children: Results of a pilot study. Psychoneuroendocrinology 20(4):439–449.

Uno H, Tarara R, Else J, Sulemen M, Sapolsky RM. 1989. Hippocampal damage associated with prolonged and fatal stress in primates. J Neurosci 9:1705–1711.

Uno H, Lohmiller L, Thieme C, Kemnitz JW, Engle MJ, Roecker EB, et al. 1990. Brain damage induced by prenatal exposure to dexamethasone in fetal rhesus macaques, 1. Hippocampus. Dev Brain Res 53:157–167.

Uno H, Eisele S, Sakai A, Shelton S, Baker E, DeJesus O, et al. 1994. Neurotoxicity of glucocorticoids in the primate brain. Horm Behav 28:336–348.

Van Os J, Selton J. 1998. Prenatal exposure to maternal stress and subsequent schizophrenia. Br J Psychiatry 172:324–326.

Van den Bergh BRH, Marcoen A. 2004. High antenatal maternal anxiety is related to ADHD symptoms, externalizing problems, and anxiety in 8- and 9-year olds. Child Dev 75(4):1085–1097.

Watson JB, Mednick SA, Huttunen M, Wang X. 1999. Prenatal teratogens and the development of adult mental illness. Dev Psychopathol 11(3):457–466.

Weinberger DR. 1995. Schizophrenia as a neurodevelopmental disorder. In: Hirsch SR, Weinberger DR, editors. Schizophrenia. Oxford: Blackwell Science.

Weinstock M. 2001. Alterations induced by gestational stress in brain morphology and behaviour of the offspring. Prog Neurobiol 65:427–451.

Weinstock M, Matlina A, Maor GI, Rosen H, McEwan BS. 1992. Prenatal stress selectively alters the reactivity of the hypothalamic–pituitary–adrenal system in the female rat. Brain Res 595:195–200.

Weiss DS, Marmar CR. 1997. The impact of event scale—revised. New York: Guilford.

Weller A, Glaubman H, Yehuda S, Caspy T, Ben-Uria Y. 1988. Acute and repeated gestational stress affect offspring learning and activity in rats. Physiol Behav 43(2):139–143.

Zelazo PR, Kearsley RB. 1980. The emergence of functional plat in infants: Evidence for a major cognitive transition. J Appl Dev Psychol 1:95–117.