THE INTERGENERATIONAL TRANSMISSION OF CHILDHOOD EXPOSURE TO VIOLENCE: BEHAVIOURAL AND BIOLOGICAL MECHANISMS

Carmine M. Pariante

INTRODUCTION

Importance

The intergenerational transmission of childhood exposure to violence has powerful clinical and social consequences, consolidating social adversity and psychopathology in future generations. The 2007 Policy Briefing by the World Health Organization Regional Office for Europe, "Preventing child maltreatment in Europe: a public health approach" (Briefing), recognizes that "there is an association between maltreatment in childhood and the risk of later … becoming a perpetrator of violence or other antisocial behaviour as a teenager or adult". The report also highlights that the costs are both overt (for example, medical care for victims, treatment of offenders and legal costs for social care) and less obvious (for example, criminal justice and prosecution costs, specialist education and mental health provision). In Europe, only the United Kingdom has calculated the total economic burden, estimated to be £735 million in 1996 (Briefing). There is no doubt that an enormous amount of work and resources are going into prevention strategies and public health approaches: however, it is surprising that very little research has been conducted in humans to try to understand why childhood maltreatment is passed from one generation to the next, and what are the biological and molecular mechanisms underlying this intergenerational effect. With the recent document on the "Grand Challenges in Global Mental Health" (Collins et al., 2011) underscoring the need for research that uses a life-course approach, and indicating the identification of "modifiable social and biological risk factors across the life course" as one of the grand challenges to be addressed urgently, this issue is also extremely timely.

Aim of this essay and summary of the findings

This essay will review the clinical evidence in relationship with the intergenerational transmission of exposure to violence. We will focus in particular on the mechanisms by which exposure to violence in the childhood of women translate into exposure to violence in their offspring, highlighting pregnancy and the "in utero" environment as the crucial timing and biological setting where these mechanisms operate. In summary, this essay will propose that experiences of childhood maltreatment in mothers induce persistent behavioural and biological changes in the regulation of maternal stress response, which in turn alter the biology of the "in utero" environment during their pregnancies, especially in more vulnerable mothers who also experience stress and depression during pregnancy. This abnormal biology of the "in utero" environment induces further changes in both mothers and offspring, which in turn contribute to the transmission of the violence exposure: in mothers, by altering the quality of the interaction with their offspring and predisposing to less vigilance and protective behaviour; and, in the offspring, by programming an altered stress response and a disturbed behavioural trajectory. Crucially, this essay will also point to the pregnancy period as a uniquely sensitive period for preventative intervention aimed at breaking the cycle of transmission.

The intergenerational transmission of exposure to violence
After years of accumulating anecdotal evidence, recently some studies have provided controlled evidence that women who experience childhood exposure to violence tend to have children who also experience exposure to violence. For example, in an American sample of almost 500 mother-child dyads, a history of maternal physical and sexual abuse was found to predict offspring maltreatment in the first two years of life, as measured by county court records of allegations and substantiations (Appleyard et al., 2011; Berlin et al., 2011). In a study conducted in the large UK cohort study, the Avon Longitudinal Study of Parents and Children, out of 14,256 children participating in the study, 293 were investigated by social services for suspected maltreatment and 115 were placed on local child protection registers; and a history of childhood abuse in parents was a risk factor for the children being investigated for maltreatment or being placed on the child protection register (Sidebotham and Heron, 2006). It is of note also our recent work conducted in the South London Child Development Study (from data collected up to offspring age 16) also reveals an association between maternal childhood maltreatment and offspring childhood maltreatment in the period from birth to eleven years (r = .24, p = 0.01; paper currently submitted). The mechanisms underlying this transmission are however unknown.

Risk factors and mechanisms for the intergenerational transmission of childhood exposure to violence
Classical risk factors for transmission of violence exposure include mothers' mental health problems, social isolation, unemployment and single parenthood (Sidebotham and Heron, 2006; Berlin et al., 2011). Appleyard et al. (Appleyard et al., 2011) identify a clear pathway from maternal sexual and physical abuse, to maternal substance use problems, to childhood victimization. Indeed, the association between psychopathology in parents and offspring exposure to maltreatment is well recognized (see also below). Interestingly, Berlin et al. (Berlin et al., 2011) identify that maternal cognitive process related to social information (hostile attributions and aggressive response biases) are also involved in the pathway between maternal exposure to violence and offspring maltreatment, thus identifying a potential mechanism. Evidence pointing to yet another, non mutually-exclusive mechanism, is that a maternal history of exposure to violence in childhood is associated with the children developing behavioral problems, which in turn may predispose them to be exposed to violence (see also "Pathway B: Child-driven" below). For example, in a large British sample of over four thousand mother-child dyads, children of mothers who experienced childhood abuse were at an elevated risk for emotional and behavioural adjustment problems at four and seven years (Roberts et al. 2004; Collishaw et al. 2007). More recently, in a Spanish study, maternal childhood abuse was found to predict symptoms of disruptive behaviour disorders in offspring during adolescence (Miranda et al. 2011). Finally, there is evidence that children's behaviour may elicit harsh discipline and abnormal parenting practices (Ge, 1996).

The contribution of the e-Risk cohort to this literature
A number of models relevant to the intergenerational transmission of violence exposure have been probed in the E-Risk cohort, especially in relationship with the role of maternal and child psychopathology in this transmission. For example, one model may suggest that families may have a genetic predisposition to use violence

as a mean of solving problems. In this regard, Jaffee et al. (Jaffee et al., 2005) have demonstrated, in the E-Risk cohort, that exposure to childhood maltreatment leads to conduct disorder only in those children who are at high genetic risk for this disorder, estimated as a function of their co-twin's conduct disorder status and the pair's zygosity. However, it is important to emphasise that the same authors also find that the "causative" pathway between child physical maltreatment to later antisocial behavior is largely environmentally-mediated (Jaffee et al., 2004b). Of note is also another study from the E-risk cohort, showing that maternal depression occurring in the 5 year after the twins' birth, but not before, is associated with child antisocial behaviour. Only approximately one third of this association is explained by the presence of a parental history of antisocial personality in depressed mother (and in the children's biological fathers) (Kim-Cohen et al., 2005). This led the authors to conclude that children exposed to maternal depression are "significantly likely to have conduct problems through a risk process that operates environmentally over any contributions of their parents' antisocial personality". Jaffee et al. have also found that environmental factors account for most of the variation in corporal punishment and physical maltreatment in the E-Risk cohort (Jaffee et al., 2004a). Thus, the role of environmental factors in this transmission cannot be underestimated.

In terms of children's exposure to violence, it is of note the study showing that children of mothers who have comorbidity (depression and antisocial disorders) have significantly higher levels of antisocial behavior when compared with children of mothers with depression only, and are at an elevated risk of experiencing multiple caregiving abuses, including physical maltreatment, high levels of maternal hostility, and exposure to domestic violence (Kim-Cohen et al., 2006). Although the model described in this paper does not directly contrast "depressed only" vs. healthy mothers, numerically there seems to be an increased rate of child exposure to violence also in the children of mothers with depression only, as shown by the almost double rates of children classified has having "probable or definitive harm" (19.4% vs. 10%), having agency involvement (18.4 % vs. 10.9%) or removed from the family (4.2% vs. 1.5%). These findings are particularly interesting in the light of our findings (discussed below) showing a relationship between depression in pregnancy and both children's psychopathology and children's exposure to maltreatment. Indeed, it is also of note another study from the E-Risk cohort, showing that, within MZ pairs, the twin receiving more maternal negativity and less warmth have more antisocial behavior problems, suggesting that maternal emotional attitudes toward children may play a causal role in the development of antisocial behavior (Caspi et al., 2004). This essay argues that one crucial mechanism by which some mothers may develop more negativity toward a specific child is the presence of depression during the pregnancy for the specific child (see "Pathway A, Mother-driven", below). With reference to the "Pathway B: Child-driven" pathway mention above (and discussed later), Jaffee et al. have also found that environmental factors account for most of the variation in corporal punishment and physical maltreatment in the E-Risk cohort: moreover, and reassuringly, a "child-driven" effect was only present for corporal punishment, not for physical maltreatment (Jaffee et al., 2004a).

Overall, it is intriguing that the above-mentioned E-Risk studies investigated (retrospectively) the occurrence of depression in the life-time of mothers using childbirth as the watershed. Therefore, it is interesting to speculate that at least some of the mother classified as "depressed in the five years after childbirth", that is, those mothers whose children show the largest impact in terms of both psychopathology and exposure to violence, might have ben also depressed during pregnancy, as

depression during pregnancy (also called depression in the antenatal period, or antenatal depression) is one of the strongest risk factors for the occurrence of depression in the first years of children' life (Hay et al., 2010).

THE ROLE OF THE ANTENATAL PERIOD

Women who have experienced childhood maltreatment tend to be depressed during pregnancy

Epidemiological and clinical studies have already described an association between experiences of childhood maltreatment and depressive symptomatology in pregnancy ("antenatal depression"), but all have examined predominantly "at risk" mothers (Romano et al., 2006; Chung et al., 2008; Rich-Edwards et al., 2011), such as pregnant adolescents or low-income women. In our recent work in the South London Child Development Study, we show an association between maternal childhood maltreatment and maternal antenatal depression in an epidemiological sample (as indicated by a positive correlation; coefficient = .38, $p < .001$; paper currently submitted).

Women depressed during pregnancy have an increased risk of their children being victims of maltreatment

The association between *lifetime* psychopathology in mothers and increased risk of childhood maltreatment in offspring has been well described. Specifically, certain parental personality attributes have been associated with offspring maltreatment, such as low self-esteem, negative affectivity (depression and anxiety), and antisocial behaviours (Oliver, 1985). More importantly, in our recent paper (Pawlby et al., 2011) we have clearly demonstrated, using data from the South London Child Development Study, that antenatal depression is associated with increased risk of the offspring

Table 2 Exposure to maternal depression *in utero* and experience of childhood maltreatment		
	Childhood maltreatment	
	No, % (*n*)	Yes, % (*n*)
Exposure to depression *in utero*		
No	84.2 (80)	15.8 (15)
Yes	60.0 (15)	40.0 (10)
χ^2 (1) = 7.03, P = 0.008.		

being subjected to childhood maltreatment (see Table). Specifically, we have found that, compared with children who had not been exposed to depression "in utero", children who were exposed were 4-times more likely to have experienced childhood maltreatment by the age of 11 years. Of note, our data point to a specific effect of antenatal, rather than postnatal, depression, in increasing the risk of childhood maltreatment (Pawlby et al., 2011). Taken together with the evidence summarised above, it is plausible that persistent behavioural and biological abnormalities in women, induced by their experience of childhood exposure to violence, increase the risk for maternal depression in pregnancy, which in turn confers risk for offspring maltreatment, and provides a vehicle for the intergenerational transmission of childhood maltreatment. However, the pathways by which this vehicle operates are yet unknown. However it is important to emphasis that our study *does not* indicate that women who are depressed during pregnancy go on to be violent to their children, as the excess of maltreatment (which, in our study, also included harsh discipline) was originated not by the mothers alone but also by other members of the family or of the social environment. However, it is possible to speculate that lack of vigilance from the mothers might have played role.

Potential pathways by which antenatal depression increases the risks of offspring maltreatment

Two, non-mutually exclusive pathways can be proposed:
- *Pathway A, Mother-Driven:* the behavioural and biological abnormalities induced by antenatal depression disrupt future maternal care, which then account for the increased risk of exposure to violence.
- *Pathway B, Child-Driven:* the behavioural and biological abnormalities induced by antenatal depression program the child onto a trajectory for behavioural problems, which then account for the increased risk of exposure to violence.

BIOLOGICAL AND BEHAVIOURAL MECHANISMS

Childhood exposure to violence induces persistent behavioural and biologic abnormalities

Both these pathways start with maternal childhood exposure to violence, and with the persistent molecular abnormalities that are induced by these experiences. Hence, we will briefly review these molecular abnormalities, before discussing the two pathways more in details. There is clear evidence that childhood maltreatment predisposes to a persistent activation of the two main biological systems involved in the stress response, the hypothalamic-pituitary-adrenal (HPA) axis and the inflammatory system. Both these systems are also hyperactive in depression, and indeed this hyperactivity is considered part of the pathogenesis of depression (Danese et al., 2007; Heim et al., 2008; Pariante and Lightman, 2008; Binder, 2009). We, and others, have extensively contributed to the understanding of the mechanism underlying HPA axis and inflammation hyperactivity in adults who experienced childhood trauma, and have proposed an explanatory model centred on the glucocorticoid receptor (GR), that is, one of the most important receptors and transcription factors governing the stress response (Danese et al., 2007; Heim et al., 2008; Pariante and Lightman, 2008; Binder, 2009). Glucocorticoid hormones, like cortisol in humans and corticosterone in rodents, are the final output of the HPA axis, and the main hormones involved in the stress response. By binding to the GR (and to the mineralocorticoid receptor, MR), cortisol effects its cellular actions, including the negative feedback regulation of the HPA axis (by which stress-induced activation of the HPA axis is followed by a rapid return to normal functioning), and the restraint of the inflammatory response (which maintains a physiological control on excessive immune processes). Although the MR is important for cortisol action, the GR is particularly relevant when the levels of glucocorticoids are high, such as during stress or depression, and thus it has traditionally been considered more relevant within this context. Childhood maltreatment has been shown to induce glucocorticoid resistance, that is, a reduction of GR function, which in turn leads to both the HPA axis hyperactivity and the increased inflammation, because of the lack of, respectively, the GR-mediated negative feedback on the HPA axis (see Figure in this page) and the GR-mediated restraint of inflammation (Danese et al., 2007; Heim et al., 2008; Pariante and Lightman, 2008; Binder, 2009). Based on this evidence, it is plausible to speculate that women who have suffered childhood exposure to violence develop glucocorticoid resistance, which in turn predisposes them to develop depression later in adult life, and especially during pregnancy, a period which naturally associated with glucocorticoid resistance (see below). Interestingly, this

hypothesis has never been tested yet.

Stress and depression during pregnancy affect the HPA axis of <u>both the mother and the child</u>

There is evidence that normal pregnancy is associated with glucocorticoid resistance, as indicated by studies showing impaired GR-mediated negative feedback regulation of the HPA axis by dexamethasone (Smith and Thomson, 1991), and reduced GR function in peripheral blood mononuclear cells (PBMCs) (Katz et al., 2011). Consistent with the presence of glucocorticoid resistance, both the HPA axis and the inflammatory system are hyperactive during normal pregnancy, and both regulate human parturition. More importantly within this context, there is also some evidence that GR resistance is more marked in women who experience depressive symptoms or stress during pregnancy, as shown by both a further reduction of GR function in PBMCs binder (Katz et al., 2011) as well as an even higher activity of the HPA axis and the inflammatory system (Coussons-Read et al., 2005; Coussons-Read et al., 2007; Christian et al., 2009; Field et al., 2009; Blackmore et al., 2011; O'Keane et al., 2011). Finally, animal and clinical studies have shown that stress during pregnancy leads to increased stress response in the offspring. Many authors have critically reviewed this literature (Weinstock, 2005; Glover et al., 2010), and overall found that stress in pregnancy tends to increase both basal- and stress-induced HPA axis activity in the offspring, and that there is concordance between maternal cortisol levels and children's cortisol levels. Although no study has examined the effects of maternal experiences of exposure to violence in childhood on offspring HPA axis, one study has found that a life-time history of maternal depression was enough to predict higher baseline cortisol in the infant (Brennan et al., 2008). Finally, it is of note that animal studies have shown that increased inflammation during gestation, via injection of lipopolysaccharide (LPS), also induces a persistent hyperactivity of the HPA axis in the offspring, as well as reduced maternal care and changes in offspring behaviour (see below) (Graciarena et al., 2010; Kentner and Pittman, 2010). It is therefore plausible that maternal experiences of childhood maltreatment (and the putative associated changes in the HPA axis and inflammation during pregnancy, especially in women who are also depressed) influence brain mechanisms relevant for stress regulation in offspring, and modify their HPA axis activity.
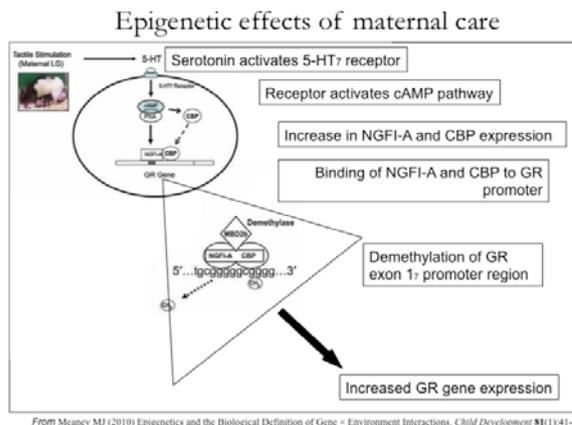
Stress and depression during pregnancy compromise maternal care via oxytocin-mediated effects (Pathway A: Mother-Driven)

Animal models have been used extensively to understand how stress during gestation alters maternal behaviour. In the best such characterised model, the rat "licking and grooming" behaviour, pregnant rats receiving a restraint stress in the last 7 days of pregnancy show, at day 6 post natal, reduced maternal care behaviour, increased HPA axis activity, and reduced brain expression of the receptor for oxytocin, a neurotransmitter regulating maternal care and social behaviour (Champagne and Meaney, 2006). These biological findings are likely related, since administration of the synthetic HPA axis hormone, dexamethasone, has also been shown to decrease oxytocin secretion, brain oxytocin receptor, and maternal care behaviour (Patchev et al., 1993). Interestingly, there are no studies testing the effects of maternal childhood maltreatment on oxytocin levels in pregnancy, although there is evidence that higher maternal oxytocin levels in pregnancy are associated with maternal bonding behaviour (Feldman et al., 2007) and are protective against the occurrence of post-natal depression (Skrundz et al., 2011). Taken together with the

evidence discussed above, these data support the notion that mothers with a history of exposure to violence in childhood, especially if also depressed, have increased HPA axis activity during pregnancy, which in turn may alter the oxytocin system and ultimately contribute to impaired maternal care.

Stress and depression during pregnancy affect offspring development and behaviour (Pathway B)

Clinical studies have shown that antenatal anxiety and depressive symptoms predict delayed motor development in infancy, and childhood emotional and behavioural problems, such as attention deficit hyperactivity disorder and disruptive behaviour

Epigenetic effects of maternal care

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disorder (Glover and O'Connor, 2002; Glover et al., 2010). Moreover, studies examining later offspring outcomes have found an association between exposure to antenatal depression/anxiety and offspring depression, antisocial behaviour and violence during adolescence (Pawlby et al., 2009; Hay et al., 2010). These studies have also demonstrated that the association between exposure to maternal psychopathology in utero and offspring psychopathology is independent from the effects of the postnatal environment, thus suggesting a "foetal programming hypothesis" (Pawlby et al., 2009; Hay et al., 2010). This advocates that the maternal biological environment "in utero" induced persistent foetal brain changes (see below). Taken together with the previously-discussed studies, it is possible to speculate that offspring of mothers with experiences of childhood maltreatment, especially if mothers have also been depressed during pregnancy, will show abnormal offspring behavioural development, which finally will predispose to exposure to exposure to violence.

Epigenetic changes in the GR mediate intergenerational programming of the stress response

In the best characterised animal model of early maltreatment, the above-mentioned rat "licking and grooming" behaviour, pups of mothers expressing low maternal care also exhibit decreased GR expression, as well as increased DNA methylation of the GR in the promoter region 1_7 (Weaver et al., 2004a; Weaver et al., 2004b) (see Figure, next page). Increased DNA methylation represses gene expression by limiting accessibility to the gene promoter and thus reducing its transcriptional activity, with the *vice versa* occurring for reduced methylation status. Indeed, *demethylation* is the process that is actively stimulated by appropriate maternal care: it is mediated by increased serotonergic transmission in the brain, and leads to increased expression of the GR and lower HPA axis activity – a protective phenotype (Weaver et al., 2004a; Weaver et al., 2004b). The absence of maternal care instead leads to a lack of demethylation, and hence less expression of the GR and high HPA axis activity. Of particular note within this experimental framework is a study showing that "high licking and grooming" mothers (i.e., good mothers) lose this behaviour toward the offspring it they are stressed during pregnancy (Champagne and Meaney, 2006). This study confirm the notion that stress (or, in humans, depression) during

pregnancy may affect subsequent maternal care, and in particular to that specific offspring. It is also of note that evidence in humans of GR epigenetic regulation by intergenerational stress is now appearing. For example, exposure to childhood maltreatment has been shown to correlate with increased methylation of the GR in post-mortem brains of suicide victims (McGowan et al., 2009), exactly at the 1_F promoter region, that is, the region equivalent to 1_7 in rodents. Even more relevant, a study found that infant offspring of mothers who had suffered from antenatal depression and anxiety have increased $GR1_F$ methylation in PBMCs from cord blood; moreover, the increased methylation correlated with increased HPA axis stress response at 3 months post partum (Oberlander et al., 2008). Finally, a recent study has found increased GR 1_F methylation in adolescent offspring of mothers who were under severe stress during pregnancy (Elbert, 2011). Collectively, these studies support the notion that the same molecular signature (epigenetic-induced reduction in GR expression and function) are present both in mothers with childhood experience of maltreatment and in their offspring – with the effects in offspring being particularly evident if mothers were also depressed during pregnancy.

CHALLENGES FOR INTERVENTION AND PREVENTION

Implications for the treatment of depression during pregnancy
Around 1-in-8 pregnant women experience a major depressive disorder (MDD) during pregnancy, and 1-in-5 experience some depressive symptoms (Grote et al., 2010). Therefore, even if depression in pregnancy is linked to a very small increase in the risk of disrupting maternal care, the sheer prevalence of this phenomenon makes it clinically relevant for the intergenerational transmission of exposure to violence. Moreover, depression in pregnancy is associated exactly to the same sociodemographic risk factors that affect intergenerational transmission of exposure to violence, such being a single mother and having a socio-economical deprived background. Both antidepressants and brief psychotherapies are effective in pregnancy, and some antidepressants are advised as preferable (Nice, 2007). However, the positive impact of a larger number of women taking antidepressants during pregnancy has to be considered against the background of small, but significantly increased, risks for the neonates, including for cardiac malformation (Reis and Kallen, 2010), pulmonary hypertension (Reis and Kallen, 2010) and, in very recent studies, for autism (Croen et al., 2011) – a "health-scare" story that has had much publicity (for example, (CNN, 2011)). Therefore, any recommendation will have enormous consequences for both future mothers and the health community.

Such a complex series of question cannot be address within a single study, and requires a variety of approaches
- Project 1: a study in pregnancy and immediate postpartum: A sample of women with a history of exposure to violence (and matched controls) <u>recruited during pregnancy</u>, and assessed, together with their infant, up to 1 year post partum. Such project would be able to address the overarching question: does a history of childhood maltreatment in women predispose to specific behavioural, biological and molecular abnormalities during pregnancy, and do these abnormalities correlate with impaired mother-infant interaction and with infants' abnormal biological and behavioural development? In most projects the assessment of maternal exposure to violence in childhood would need to be conducted retrospectively, but it is also

possible to envisage an assessment of pregnant young adults belonging to ongoing longitudinal cohorts (such as E-risk or Dunedin) where childhood data have been assessed prospectively. Moreover, such studies would need to prioritise proxy measures of risk factors for childhood exposure to violence, since offspring will be assessed as infants. For example, such studies may assess mother-infant interaction, or parenting style. This is because accruing cases of real exposure to violence in the offspring would require very large cohorts and long follow-up into childhood and adolescence.

- Project 2: a study in young adults: A cohort of young adults <u>who have been assessed longitudinally since childhood, and who are the offspring of mothers who were exposed to violence in childhood</u>. Such project would address the overarching question: do young adults whose mothers experienced childhood maltreatment have specific behavioural, biological and molecular abnormalities, and do these abnormalities correlate with maternal features? Such study would be more challenging. A novel cohort of young adults purposely recruited at present would require that <u>both</u> the assessment of maternal mental state in pregnancy (20 or more years ago) <u>and</u> of maternal exposure to violence in childhood (40 or more years ago) are conducted retrospectively. However, there is also the possibility of using existing longitudinal cohorts of children whose mothers were recruited and assessed during pregnancy, such as the South London Child Development Study (where subjects are now age 25) or the ALSPAC study (where subjects have just become adults), but even in this case the maternal exposure to violence in childhood has been conducted (or would need to be conducted) retrospectively.

INTER-GENERATIONAL TIME-LINE					
MOTHERS	**Childhood and Adolescence**	**Pregnancy**	**Post-Partum**	**Late Adulthood**	**Middle-age**
OFFSPRING		**In Utero**	**Early Development**	**Childhood And Adolescence**	**Adulthood**
Project 1					
Measures in Mothers	*Collected Retrospectively*	***Recruitment Now***	*Assessed Prospectively*		
Measures in Offspring			*Assessed Prospectively*		
Project 2					
Measures in Mothers	*Collected Retrospectively*	***Recruitment 20 Years Ago***	*Assessed Prospectively*	*Assessed Prospectively*	*Assessed Prospectively*
Measures in Offspring			*Assessed Prospectively*	*Assessed Prospectively*	*Assessed Prospectively*

- Project 3: animal and experimental models: This represent yet another approach to dissect some of these questions, both in terms of assessing brain-relevant molecular mechanisms (i.e., accessing tissues not otherwise available in humans) and of controlling exposures in an experimental fashion. Animal studies are of course less ecologically relevant when compared to the richness of the human experience, but allow ethical manipulation of the environment. For example, the previously mentioned animal study has shown that exposure of "high licking and grooming" (good mothers) to stress in pregnancy make them "less caring" – but no studies, to our knowledge, has tested the opposite effects: can enriched environment during pregnancy reverse the "low licking and grooming" (bad mothers) behaviour. Moreover, animal models can be used to test whether pharmacological treatment can affect maternal care, hence identifying targets for therapeutic interventions. A final

advantage of using experimental models is that of generating (at relatively low costs) novel molecular targets (for example, through -omics approaches) that can then be examined in the more expensive (and precious) human blood. Such project would address the overarching question: what are the molecular mechanisms (at the level of receptor, second messengers, transcription factors, and cellular pathways) by which the maternal biological environment during pregnancy leads to changes in the offspring brain, and can these novel mechanism been replicated in clinical samples?

Conclusions

This essay proposes that the pregnancy and the "in utero" environment as the crucial *timing* and *biological setting* where the intergenerational transmission of childhood exposure to violence occurs. While there has been extensive research on <u>both</u> the persistent biological effects of exposure to violence <u>and</u> the role of the in utero environment on offspring outcome, there is a lack of research putting these two areas together, and using a <u>fully</u> <u>integrated approach, including clinical and psychosocial assessments, blood and saliva biomarkers, gene expression and epigenetics</u>. Of course, while studying "risk" mechanisms, this research will also be able to identify <u>protective factors</u> that prevent the intergenerational transmission, and ultimately generate novel therapeutic pathways that will break the intergenerational transmission.

REFERENCES

Appleyard, K., Berlin, L. J., Rosanbalm, K. D., Dodge, K. A. 2011. Preventing early child maltreatment: implications from a longitudinal study of maternal abuse history, substance use problems, and offspring victimization. Prev Sci 12, 139-149.

Berlin, L. J., Appleyard, K., Dodge, K. A. 2011. Intergenerational continuity in child maltreatment: mediating mechanisms and implications for prevention. Child Dev 82, 162-176.

Binder, E. B. 2009. The role of FKBP5, a co-chaperone of the glucocorticoid receptor in the pathogenesis and therapy of affective and anxiety disorders. Psychoneuroendocrinology 34 Suppl 1, S186-195.

Blackmore, E. R., Moynihan, J. A., Rubinow, D. R., Pressman, E. K., Gilchrist, M., O'Connor, T. G. 2011. Psychiatric symptoms and proinflammatory cytokines in pregnancy. Psychosom Med 73, 656-663.

Brennan, P. A., Pargas, R., Walker, E. F., Green, P., Newport, D. J., Stowe, Z. 2008. Maternal depression and infant cortisol: influences of timing, comorbidity and treatment. J Child Psychol Psychiatry 49, 1099-1107.

Briefing, P. *Preventing child maltreatment in Europe: a public health approach* Copenhagen, Denmark.

Caspi, A., Moffitt, T. E., Morgan, J., Rutter, M., Taylor, A., Arseneault, L., Tully, L., Jacobs, C., Kim-Cohen, J., Polo-Tomas, M. 2004. Maternal expressed emotion predicts children's antisocial behavior problems: using monozygotic-twin differences to identify environmental effects on behavioral development. Developmental psychology 40, 149-161.

Champagne, F. A., Meaney, M. J. 2006. Stress during gestation alters postpartum maternal care and the development of the offspring in a rodent model. Biol Psychiatry 59, 1227-1235.

Christian, L. M., Franco, A., Glaser, R., Iams, J. D. 2009. Depressive symptoms are associated with elevated serum proinflammatory cytokines among pregnant women. Brain Behav Immun 23, 750-754.

Chung, E. K., Mathew, L., Elo, I. T., Coyne, J. C., Culhane, J. F. 2008. Depressive symptoms in disadvantaged women receiving prenatal care: the influence of adverse and positive childhood experiences. Ambul Pediatr 8, 109-116.

CNN (2011). Antidepressant use in pregnancy may raise autism risk.

Collins, P. Y., Patel, V., Joestl, S. S., March, D., Insel, T. R., Daar, A. S., Anderson, W., Dhansay, M. A., Phillips, A., Shurin, S., Walport, M., Ewart, W., Savill, S. J., Bordin, I. A., Costello, E. J., Durkin, M., Fairburn, C., Glass, R. I., Hall, W., Huang, Y., Hyman, S. E., Jamison, K., Kaaya, S., Kapur, S., Kleinman, A., Ogunniyi, A., Otero-Ojeda, A., Poo, M. M., Ravindranath, V., Sahakian, B. J., Saxena, S., Singer, P. A., Stein, D. J. 2011. Grand challenges in global mental health. Nature 475, 27-30.

Coussons-Read, M. E., Okun, M. L., Schmitt, M. P., Giese, S. 2005. Prenatal stress alters cytokine levels in a manner that may endanger human pregnancy. Psychosom Med 67, 625-631.

Coussons-Read, M. E., Okun, M. L., Nettles, C. D. 2007. Psychosocial stress increases inflammatory markers and alters cytokine production across pregnancy. Brain Behav Immun 21, 343-350.

Croen, L. A., Grether, J. K., Yoshida, C. K., Odouli, R., Hendrick, V. 2011. Antidepressant use during pregnancy and childhood autism spectrum disorders. Arch Gen Psychiatry 68, 1104-1112.

Danese, A., Pariante, C. M., Caspi, A., Taylor, A., Poulton, R. 2007. Childhood maltreatment predicts adult inflammation in a life-course study. Proc.Natl.Acad.Sci.U.S.A 104, 1319-1324.

Elbert, K. R. M. R. H. G. K. D. M. S. A. M. a. T. 2011. Transgenerational impact of intimate partner violence on methylation in the promoter of the glucocorticoid receptor. Translational Psychiatry doi:10.1038/tp.2011.21.

Feldman, R., Weller, A., Zagoory-Sharon, O., Levine, A. 2007. Evidence for a neuroendocrinological foundation of human affiliation: plasma oxytocin levels across pregnancy and the postpartum period predict mother-infant bonding. Psychol Sci 18, 965-970.

Field, T., Diego, M., Hernandez-Reif, M., Deeds, O., Holder, V., Schanberg, S., Kuhn, C. 2009. Depressed pregnant black women have a greater incidence of prematurity and low birthweight outcomes. Infant Behav.Dev. 32, 10-16.

Ge, X. C., Rand D.; Cadoret, Remi J.; Neiderhiser, Jenae M.; Yates, William; Troughton, Edward; Stewart, Mark A. 1996. The developmental interface between nature and nurture: A mutual influence model of child antisocial behavior and parent behaviors. Developmental Psychology 32, 574-589.

Glover, V., O'Connor, T. G. 2002. Effects of antenatal stress and anxiety: Implications for development and psychiatry. British Journal of Psychiatry 180, 389-391.

Glover, V., O'Connor, T. G., O'Donnell, K. 2010. Prenatal stress and the programming of the HPA axis. Neurosci Biobehav Rev 35, 17-22.

Graciarena, M., Depino, A. M., Pitossi, F. J. 2010. Prenatal inflammation impairs adult neurogenesis and memory related behavior through persistent hippocampal TGFbeta1 downregulation. Brain Behav Immun 24, 1301-1309.

Grote, N. K., Bridge, J. A., Gavin, A. R., Melville, J. L., Iyengar, S., Katon, W. J. 2010. A meta-analysis of depression during pregnancy and the risk of preterm birth, low birth weight, and intrauterine growth restriction. Arch Gen Psychiatry 67, 1012-1024.

Hay, D. F., Pawlby, S., Waters, C. S., Perra, O., Sharp, D. 2010. Mothers' antenatal depression and their children's antisocial outcomes. Child Dev 81, 149-165.

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, 693-710.

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, 1047-1058.

Jaffee, S. R., Caspi, A., Moffitt, T. E., Taylor, A. 2004b. Physical maltreatment victim to antisocial child: evidence of an environmentally mediated process. J Abnorm Psychol 113, 44-55.

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. Dev Psychopathol 17, 67-84.

Katz, E. R., Stowe, Z. N., Newport, D. J., Kelley, M. E., Pace, T. W., Cubells, J. F., Binder, E. B. 2011. Regulation of mRNA expression encoding chaperone and co-chaperone proteins of the glucocorticoid receptor in peripheral blood: association with depressive symptoms during pregnancy. Psychol Med1-14.

Kentner, A. C., Pittman, Q. J. 2010. Minireview: early-life programming by inflammation of the neuroendocrine system. Endocrinology 151, 4602-4606.

Kim-Cohen, J., Moffitt, T. E., Taylor, A., Pawlby, S. J., Caspi, A. 2005. Maternal depression and children's antisocial behavior: nature and nurture effects. Arch Gen Psychiatry 62, 173-181.

Kim-Cohen, J., Caspi, A., Rutter, M., Tomas, M. P., Moffitt, T. E. 2006. The caregiving environments provided to children by depressed mothers with or without an antisocial history. Am J Psychiatry 163, 1009-1018.

McGowan, P. O., Sasaki, A., D'Alessio, A. C., Dymov, S., Labonte, B., Szyf, M., Turecki, G., Meaney, M. J. 2009. Epigenetic regulation of the glucocorticoid receptor in human brain associates with childhood abuse. Nat Neurosci 12, 342-348.

Nice (2007). Antenatal and postnatal mental health: Alden Press, Great Britain.

O'Keane, V., Lightman, S., Marsh, M., Pawlby, S., Papadopoulos, A. S., Taylor, A., Moore, R., Patrick, K. 2011. Increased pituitary-adrenal activation and shortened gestation in a sample of depressed pregnant women: A pilot study. J Affect Disord 130, 300-305.

Oberlander, T. F., Weinberg, J., Papsdorf, M., Grunau, R., Misri, S., Devlin, A. M. 2008. Prenatal exposure to maternal depression, neonatal methylation of human glucocorticoid receptor gene (NR3C1) and infant cortisol stress responses. Epigenetics 3, 97-106.

Oliver, J. E. 1985. Successive generations of child maltreatment: social and medical disorders in the parents. Br J Psychiatry 147, 484-490.

Pariante, C. M., Lightman, S. L. 2008. The HPA axis in major depression: classical theories and new developments. Trends in Neurosciences 31, 464-468.

Patchev, V. K., Schlosser, S. F., Hassan, A. H., Almeida, O. F. 1993. Oxytocin binding sites in rat limbic and hypothalamic structures: site-specific modulation by adrenal and gonadal steroids. Neuroscience 57, 537-543.

Pawlby, S., Hay, D. F., Sharp, D., Waters, C. S., O'Keane, V. 2009. Antenatal depression predicts depression in adolescent offspring: prospective longitudinal community-based study. J Affect Disord 113, 236-243.

Pawlby, S., Hay, D., Sharp, D., Waters, C. S., Pariante, C. M. 2011. Antenatal depression and offspring psychopathology: the influence of childhood maltreatment. Br J Psychiatry.

Reis, M., Kallen, B. 2010. Delivery outcome after maternal use of antidepressant drugs in pregnancy: an update using Swedish data. Psychol Med1-11.

Rich-Edwards, J. W., James-Todd, T., Mohllajee, A., Kleinman, K., Burke, A., Gillman, M. W., Wright, R. J. 2011. Lifetime maternal experiences of abuse and risk of pre-natal depression in two demographically distinct populations in Boston. Int J Epidemiol 40, 375-384.

Romano, E., Zoccolillo, M., Paquette, D. 2006. Histories of child maltreatment and psychiatric disorder in pregnant adolescents. J Am Acad Child Adolesc Psychiatry 45, 329-336.

Sidebotham, P., Heron, J. 2006. Child maltreatment in the "children of the nineties": a cohort study of risk factors. Child Abuse Negl 30, 497-522.

Skrundz, M., Bolten, M., Nast, I., Hellhammer, D. H., Meinlschmidt, G. 2011. Plasma oxytocin concentration during pregnancy is associated with development of postpartum depression. Neuropsychopharmacology 36, 1886-1893.

Smith, R., Thomson, M. 1991. Neuroendocrinology of the hypothalamo-pituitary-adrenal axis in pregnancy and the puerperium. Baillieres Clin Endocrinol Metab 5, 167-186.

Weaver, I. C., Cervoni, N., Champagne, F. A., D'Alessio, A. C., Sharma, S., Seckl, J. R., Dymov, S., Szyf, M., Meaney, M. J. 2004a. Epigenetic programming by maternal behavior. Nat Neurosci 7, 847-854.

Weaver, I. C., Diorio, J., Seckl, J. R., Szyf, M., Meaney, M. J. 2004b. Early environmental regulation of hippocampal glucocorticoid receptor gene expression: characterization of intracellular mediators and potential genomic target sites. Ann N Y Acad Sci 1024, 182-212.

Weinstock, M. 2005. The potential influence of maternal stress hormones on development and mental health of the offspring. Brain Behav Immun 19, 296-308.