



Citation for published version:

Turner-Cobb, J, Jessop, DS & Lightman, S 2012, 'Effects of childhood stress: hardwired or reversible?', *The Biologist*, vol. 59, no. 4, pp. 31-35.

Publication date:
2012

Document Version
Peer reviewed version

[Link to publication](#)

University of Bath

General rights

Copyright and moral rights for the publications made accessible in the public portal are retained by the authors and/or other copyright owners and it is a condition of accessing publications that users recognise and abide by the legal requirements associated with these rights.

Take down policy

If you believe that this document breaches copyright please contact us providing details, and we will remove access to the work immediately and investigate your claim.

ARTICLE FOR THE BIOLOGIST

EFFECTS OF CHILDHOOD STRESS: HARDWIRED OR REVERSIBLE?

Julie M Turner-Cobb¹, David S Jessop² and Stafford L Lightman²

¹Dept of Psychology, University of Bath, Claverton Down, Bath BA2 7AY

²Henry Wellcome Laboratories for Integrative Neuroscience and Endocrinology, Dorothy Hodgkin Building, University of Bristol, Whitson Street, Bristol BS1 3NY

The ability to adapt to a changing environment is of paramount importance both for the survival of the individual and for the success of species (McEwen, 2007). At the level of the individual, it is important to have a stress-response system that can protect against predators, changes in climatic conditions and food availability, and internal stressors such as infection or blood loss (Lightman, 2008). At a population level, it is the combination of individual survival and ability to reproduce that will determine evolutionary success.

The neuroendocrine system is a major factor in an individual's ability to maintain homeostasis and optimal function of cognitive and metabolic activities. The flip side of this ability to respond to stress in a protective manner is that over activation of this same neuroendocrine stress response can actually result in increased morbidity and mortality from metabolic, cardiovascular and psychological disease.

It has now been increasingly recognised that exposure of young animals to adverse conditions not only results in a stress response at that time but can programme the animal's neuroendocrine, metabolic, behavioural and immunological responses for the rest of that animal's life. This permanent imprinting of an animal's behaviour is most sensitive in early life and is known as programming (Barker, 1999). Our current concept of this is that poor intrauterine or postnatal conditions result in epigenetic changes-changes in gene expression caused by mechanisms other than changes in the underlying DNA sequence - which contribute to altered gene function throughout the rest of the life of the animal (Heim, 2012). Many animal models have been developed to explore the mechanisms and outcomes of perinatal programming. The offspring of stressed mothers have been shown to develop altered stress responses (Maccari, 1995) and even changes in maternal behaviour are sufficient to cause significant epigenetic changes in their offspring (Weaver, 2004). In man, both pre and postnatal maternal anxiety and depression are sufficient to result in sustained programming effects on the autonomic nervous system and hypothalamic-pituitary-adrenal (HPA) axis of the offspring (Vedhara, 2012).

Glucocorticoids – the steroid hormones secreted from the adrenal cortex – appear to be very important mediators of stress-induced perinatal programming. Many studies have shown that antenatal treatment with glucocorticoids results in decreased birth weight and abnormal HPA axis activity in later life (Kapoor, 2008) as well as being associated with increased risk of cardiovascular disease and the development of affective disorder (Seckl, 2004).

The mechanisms underlying perinatal programming appear to involve dysregulation of the placental enzyme 11 β -hydroxysteroid dehydrogenase type 2 which normally protects the foetus from maternal cortisol (Wyrwoll, 2009). The end result is that the foetus, on exposure to high levels of cortisol develops epigenetic changes in glucocorticoid receptors. This has been found both in rats (McCormick, 2000) and in man (McGowan, 2009).

Positive and Negative Effects of Stress in Human Childhood

Fast forward from the prenatal period into the first few years of childhood and it is still possible to observe these epigenetic alterations/perinatal programming of the stress response. In concert with life experience and stress exposure, these shape physiological reactivity and health outcome throughout adult life.

The early years of childhood are a critical period for the influence of stress exposure on future health (Coe, 2003). The most graphic demonstration of the importance of maternal attachment for psychological and physical health in young infants is Harlow's well-known attachment experiments (Harlow, 1959; Meyer, 1975) in which infant monkeys were experimentally orphaned and reared by surrogate machine mothers. In children, work at the more severe end of the early life adversity spectrum has drawn from examples of childhood physical, emotional or sexual maltreatment, including examples of children being institutionalised in extremely deprived orphanage environments. Such work has revealed the most striking dysregulatory effects on neuroendocrine functioning (Carrion, 2002; Cicchetti, 2001; Gunnar, 2001). Whilst in the more severe orphanage cases a flatter diurnal profile and higher cortisol levels have been reported (Gunnar, 2001), the direction of this dysregulation is not consistent across the range of maltreatment experiences. Hypo- or hypercortisolism appears to depend upon the severity of the experience, duration of the stressor, age of the child during stressor exposure and timing of the neuroendocrine or health outcome assessed (Turner-Cobb, 2005). Less severe but still producing notable effects which are often delayed or long lasting is the effect of family functioning, in particular the maternal psychological state, on glucocorticoid regulation in young children. For example, the cortisol response of seven year old children experiencing an acute mild laboratory stressor was significantly greater in those who had been exposed to maternal clinical depression during the first two years of life (Ashman, 2002). Temperament seems to compound the relationship between

early life adversity and physical response with children who exhibit more introverted or internalising behaviours having elevated cortisol responses (Ashman et al, 2002). This trajectory of stress effects has been reported to extend into adolescence, with 13 year olds exposed to early life adversity in the form of post natal depression having significantly higher morning cortisol levels compared to controls (Halligan, 2004).

Work in two particular areas of life events/potential stressors has enabled researchers to place stress responses in young children under the microscope in key naturalistic settings. The first of these is the experience of childcare (ie non-maternal group care away from the maternal home, either in a home environment with a child minder or in an institutionalised nursery or preschool environment). A fundamental difference is the lack of one-to-one maternal care and the replacement with group care with other children and often a range of carers.

Childcare received some rather bad press back in the 1980's and 90's with anecdotal horror stories of the emotional damage caused by out of home childcare experiences. Such accounts generated a wealth of research to scientifically examine the true toll of childcare. Important work in this area has identified low quality childcare, particularly in conjunction with certain types of temperament to have negative effects on the developing neuroendocrine system (Dettling, 2000). Quality of care received, coupled with temperaments of negative affectivity (greater fear, anger, discomfort) and lower effortful control (impulse control), was found to be related to cortisol increases over the day (Dettling, 2000). Increases in cortisol have been observed in the afternoon period when a decline would have been expected (Watanura, 2003). Yet it's not just the more shy or introverted children who respond more to the demands of childcare. HPA axis responses have also been active in more extroverted children in these circumstances, suggesting the cause of cortisol dysregulation to be a mismatch between environment and individual temperament (Watanura, 2003; Zimmermann, 2004).

There is a paucity of research that has looked longitudinally at the effects of childcare on health. A birth cohort study by Ball and colleagues (Ball, 2002) provides evidence that childcare experience may confer physiological benefits in terms of fighting infection. Children up to the age of three years who attended larger childcare facilities with six or more unrelated children were more likely to have a cold during the preschool years (Ball, 2002). However, they were less likely to have a cold during their formal school career up until the age of 13 when the chances of getting a cold equalled that of other children who had either not attended preschool or attended smaller childcare environments.

The consensus of this work then is that high quality childcare does not have negative effects on children in terms of their physical or psychological health and in fact may confer improved neurobiological outcomes with implications for physical health in subsequent years. Work in our laboratory also suggests that in children whose mothers were less satisfied in their work, the experience of childcare may be beneficial in preventing hypercortisol responses (Chryssanthopoulou, 2005).

The other key naturally occurring life event for the majority of children in developed countries is that of the experience of starting school. This can be considered a naturalistic stressor as it involves the child entering a new social environment, engaging with teachers and peers in a relatively formal setting with the accompanying unpredictable and uncontrollable demands of adapting to a new physical environment and routine. Does the experience of starting school increase stress hormone levels and disrupt immunity to the degree which might influence health? Early work in the 1990's suggested this was the case (Boyce, 1995) and more recent work has found cortisol at school transition to be elevated if the child had less preschool experience (Quas, 2002). Our research group has conducted longitudinal work examining cortisol levels in children starting school at age four (Turner-Cobb, 2008). Controlling for childcare experience we found an anticipatory increase in mean diurnal cortisol levels up to six months before starting school, as well as an increase at transition, followed by an adaptive decline in cortisol levels six months later (Turner-Cobb et al, 2008). We also found associations between higher cortisol and more extrovert or impulsive temperaments and an interaction between more extroverted temperaments and the experience of social isolation being associated with higher cortisol six months after transition (Turner-Cobb et al, 2008). Prenatal stress has also been found to predict cortisol stress reactivity in five year old children starting their second year of schooling (Gutteling, 2005). In respect to health, in our transition study we found that higher cortisol at transition was associated with fewer colds over the following six months, indicating that the acute stress associated with starting school may prime the immune system to develop resistance to infection (Turner-Cobb,2011). This fits with the idea that whilst enduring or chronic stress may be damaging to health, acute stress may in some instances upregulate immune responses, an idea consistent with early stress work in adults (Selye, 1976) and work in animals (Dhabhar, 1997).

These early experiences of stress may shape our psychoendocrine-immune profile. What happens if we take a much broader perspective on the effect of early experience and move beyond these more immediate timeframe effects? What is the degree of plasticity within physiological systems such as the stress response and when might the more severe experiences have long lasting effects? There is early evidence to suggest that early life

experiences can have an influence on our physiology and health well into adulthood. For example, in young adult women who had experienced childhood sexual or physical abuse, dexamethasone suppression of cortisol was observed in only those who also had a psychiatric diagnosis (Newport, 2004). This work suggests that early life stress can create a vulnerability to subsequent glucocorticoid dysregulation the outcome of which is determined by subsequent life events and responses to them. Indeed such epigenetic effects even appear to operate across generations, with reports of glucocorticoid alterations in adult children of parents who experienced severely stressful life events (Yehuda, 2001).

There is also evidence using a variety of inflammatory markers including C-reactive protein, interleukin-6 and tumour necrosis factor that adversity during childhood may increase vulnerability to inflammatory diseases in later life. For example, low socioeconomic status (SES) experienced at age 2-3 years has been associated with proinflammatory markers in adolescence (Miller, 2007), low SES and emotional difficulties at age seven have both been associated with raised inflammatory responses in middle age (Appleton, 2012) and greater severity of childhood adversity from a range of causes has been associated with greater inflammatory responses and reduced life span in older age when combined with subsequent life stress such as caregiving (Kiecolt-Glaser, 2011).

In conclusion, although there is some indication that changes in physiological functioning as a result of early life stress can become hardwired and resistant to restoration to normal functioning even when replaced by a more favourable environment in adulthood (Miller, 2007), we do not know enough about the underlying mechanisms to conclude that these are indeed irreversible. There is clear social need for early intervention in vulnerable or at risk children (Gunnar, 2001) and intervention may prevent pathological consequences in adulthood of chronic glucocorticoid exposure such as autoimmune disease (Dube, 2009), cardiovascular disease (Roy, 2010); and chronic pain conditions (Nicolson, Davis, Kruszewski, 2010). The key questions to address now are: when does a healthy stress response in developing children (required to facilitate optimum adaptation to cope with life's challenges) tip into an inappropriate and damaging response (precipitated by severe, enduring or repeated stressors coupled with early adversity) and what is the degree of plasticity within this extremely delicate balance of neuroendocrine and immune factors?

References

- Appleton AA, Buka SL, McCormick MC, Koenen, KC Loucks EB, & Kubzansky LD (2012). The Association Between Childhood Emotional Functioning and Adulthood Inflammation Is Modified by Early-Life Socioeconomic Status. *Health Psychol*.
- Ashman SB, Dawson G, Panagiotides H, Yamada E, & Wilkinson CW (2002). Stress hormone levels of children of depressed mothers. *Development and Psychopathology*, 14(2), 333-349.
- Ball TM, Holberg CJ, Aldous MB, Martinez FD, & Wright AL (2002). Influence of attendance at day care on the common cold from birth through 13 years of age. *Archives of Pediatrics & Adolescent Medicine*, 156(2), 121-126.
- Barker DJ (1999). Fetal origins of cardiovascular disease. *Ann Med*, 31 Suppl 1:3-6.
- Boyce WT, Champoux M, Suomi SJ, & Gunnar MR (1995). Salivary cortisol in nursery-reared rhesus monkeys: reactivity to peer interactions and altered circadian activity. *Developmental Psychobiology*, 28(5), 257-267.
- Carrion VG, Weems CF, Ray RD, Glaser B, Hessl D, & Reiss AL (2002). Diurnal salivary cortisol in pediatric posttraumatic stress disorder. *Biological Psychiatry*, 51(7), 575-582.
- Chryssanthopoulou CC, Turner-Cobb JM, Lucas A, & Jessop D (2005). Childcare as a stabilizing influence on HPA axis functioning: a reevaluation of maternal occupational patterns and familial relations. *Dev Psychobiol*, 47(4), 354-368.
- Cicchetti D, & Rogosch FA (2001). Diverse patterns of neuroendocrine activity in maltreated children. *Development and Psychopathology*, 13(3), 677-693.
- Coe CL, & Lubach GR (2003). Critical periods of special health relevance for psychoneuroimmunology. *Brain Behav Immun*, 17(1), 3-12.
- Cohen S, Hamrick N, Rodriguez MS, Feldman PJ, Rabin BS, & Manuck SB (2002). Reactivity and vulnerability to stress-associated risk for upper respiratory illness. *Psychosom Med*, 64(2), 302-310.
- Dahl RE, & Gunnar MR (2009). Heightened stress responsiveness and emotional reactivity during pubertal maturation: implications for psychopathology. *Dev Psychopathol*, 21(1), 1-6.
- Dettling AC, Parker SW, Lane S, Sebanc A, & Gunnar MR (2000). Quality of care and temperament determine changes in cortisol concentrations over the day for young children in childcare. *Psychoneuroendocrinology*, 25(8), 819-836.
- Dhabhar FS, & McEwen BS (1997). Acute stress enhances while chronic stress suppresses cell-mediated immunity in vivo: a potential role for leukocyte trafficking. *Brain, Behavior, And Immunity*, 11(4), 286-306.
- Dube SR, Fairweather D, Pearson WS, Felitti VJ, Anda RF, & Croft JB (2009). Cumulative childhood stress and autoimmune diseases in adults. *Psychosom Med*, 71(2), 243-250.
- Gunnar MR, Morison SJ, Chisholm K, & Schuder M (2001). Salivary cortisol levels in children adopted from Romanian orphanages. *Development and Psychopathology*, 13(3), 611-628.
- Gunnar MR, & Vazquez DM (2001). Low cortisol and a flattening of expected daytime rhythm: potential indices of risk in human development. *Development and Psychopathology*, 13(3), 515-538.
- Gutteling BM, Weerth CD, & Buitelaar JK (2005). Prenatal stress and children's cortisol reaction to the first day of school. *Psychoneuroendocrinology*, 30(6), 541-549.
- Halligan SL, Herbert J, Goodyer IM, & Murray L (2004). Exposure to Postnatal Depression Predicts Elevated Cortisol in Adolescent Offspring. *Biological Psychiatry*, 55(4), 376-381.
- Harlow HF, & Zimmermann RR (1959). Affectional responses in the infant monkey; orphaned baby monkeys develop a strong and persistent attachment to inanimate surrogate mothers. *Science*, 130(3373), 421-432.

- Heim C & Binder EB (2012). Current research trends in early life stress and depression: review of human studies on sensitive periods, gene-environment interactions, and epigenetics. *Exp Neurol*. 233: 102-111.
- Kapoor A, Petropoulos S, Matthews SG (2008). Fetal programming of hypothalamic-pituitary-adrenal (HPA) axis function and behavior by synthetic glucocorticoids. *Brain Res Rev*, 57:586-595.
- Kiecolt-Glaser JK, Gouin JP, Weng NP, Malarkey WB, Beversdorf DQ, & Glaser R (2011). Childhood adversity heightens the impact of later-life caregiving stress on telomere length and inflammation. *Psychosom Med*, 73(1), 16-22.
- Lightman SL (2008). The neuroendocrinology of stress: a never ending story. *J Neuroendocrinol*; 20(6):880-4.
- Maccari S, Piazza PV, Kabbaj M, Barbazanges A, Simon H, Le Moal M (1995). *J Neurosci*; 15:110-116.
- Meyer JS, Novak MA, Bowman RE, & Harlow HF (1975). Behavioral and hormonal effects of attachment object separation in surrogate-peer-reared and mother-reared infant rhesus monkeys. *Dev Psychobiol*, 8(5), 425-435.
- McCormick JA, Lyons V, Jacobson MD, Noble J, Diorio J, Nyirenda M, Weaver S, Ester W, Yau JL, Meaney MJ, Seckl JR, Chapman KE (2000). 5'-heterogeneity of glucocorticoid receptor messenger RNA is tissue specific: differential regulation of variant transcripts by early-life events. *Mol Endocrinol*; 14:506-517.
- McEwen BS (2007). Physiology and neurobiology of stress and adaptation: central role of the brain. *Physiol Rev*, 87:873-904.
- McGowan PO, Sasaki A, D'Alessio AC, Dymov S, Labonté B, Szyf M, Turecki G, Meaney MJ (2009). Epigenetic regulation of the glucocorticoid receptor in human brain associates with childhood abuse. *Nat Neurosci*; 12:342-348.
- Miller G, & Chen E (2007). Unfavorable socioeconomic conditions in early life presage expression of proinflammatory phenotype in adolescence. *Psychosom Med*, 69(5), 402-409.
- Newport DJ, Heim C, Bonsall R, Miller AH, & Nemeroff CB (2004). Pituitary-adrenal responses to standard and low-dose dexamethasone suppression tests in adult survivors of child abuse. *Biological Psychiatry*, 55, 10-20.
- Nicolson NA, Davis MC, Kruszewski D, & Zautra AJ (2010). Childhood maltreatment and diurnal cortisol patterns in women with chronic pain. *Psychosom Med*, 72(5), 471-480.
- Quas JA, Murowchick E, Bensadoun J, & Boyce WT (2002). Predictors of children's cortisol activation during the transition to kindergarten. *Developmental and Behavioral Pediatrics*, 23(5), 304-313.
- Roy A, Janal MN, & Roy M (2010). Childhood trauma and prevalence of cardiovascular disease in patients with type 1 diabetes. *Psychosom Med*, 72(8), 833-838.
- Seckl JR (2004). Prenatal glucocorticoids and long-term programming. *Eur J Endocrinol*; 151 Suppl 3:U49-62.
- Selye H (1976). *The Stress of Life*. New York: McGraw-Hill.
- Turner-Cobb JM (2005). Psychological and stress hormone correlates in early life: a key to HPA-axis dysregulation and normalisation. *Stress*, 8(1), 47-57.
- Turner-Cobb JM, Rixon L & Jessop DS (2008). A prospective study of diurnal cortisol responses to the social experience of school transition in four-year-old children: anticipation, exposure, and adaptation. *Dev Psychobiol*, 50(4), 377-389.
- Turner-Cobb JM, Rixon L, & Jessop DS (2011). Hypothalamic-pituitary-adrenal axis activity and upper respiratory tract infection in young children transitioning to primary school. *Psychopharmacology (Berl)*, 214(1), 309-317.
- Vedhara K, Metcalfe C, Brant H, Crown A, Northstone K, Dawe K, Lightman S, Davey Smith G (2012). Maternal mood and neuroendocrine programming: effects of time of exposure and sex. *Journal of Neuroendocrinology* (in press)

- Watanabe SE, Donzella B, Alwin J, & Gunnar MR (2003). Morning-to-Afternoon Increases in Cortisol Concentrations for Infants and Toddlers at Child Care: Age Differences and Behavioral Correlates. *Child Development, 74*(4), 1006-1020.
- Weaver IC, Cervoni N, Champagne FA, D'Alessio AC, Sharma S, Seckl JR, Dymov S, Szyf M, Meaney MJ (2004). Epigenetic programming by maternal behavior. *Nat Neurosci, 7*:847-854.
- Wegman HL, & Stetler C (2009). A meta-analytic review of the effects of childhood abuse on medical outcomes in adulthood. *Psychosom Med, 71*(8), 805-812.
- Wyrwoll CS, Seckl JR, Holmes MC (2009). Altered placental function of 11beta-hydroxysteroid dehydrogenase 2 knockout mice *Endocrinology, 150*:1287-1293
- Yehuda R, Halligan SL, & Grossman R (2001). Childhood trauma and risk for PTSD: Relationship to intergenerational effects of trauma, parental PTSD, and cortisol excretion. *Development and Psychopathology, 13*(3), 733-753.
- Zimmermann LK & Stansbury K (2004). The influence of emotion regulation, level of shyness, and habituation on the neuroendocrine response of three-year-old children. *Psychoneuroendocrinology, 29*, 973-982.