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Biological embedding of early childhood adversity: Toxic stress and the vicious cycle of poverty in South Africa

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Introduction

Poverty impacts a wide range of child development outcomes. Its effects endure across individual lives and through generations (McLoyd, 1998). Poverty in South Africa is often accompanied by poor housing, unemployment, lack of clean water, air pollution, noise, crowding, chronic safety fears, malnutrition, HIV and TB, exposure to environmental toxins, physical hazards, poor healthcare, poor education and lack of adequate childcare. Social maladies such as domestic violence, neighbourhood violence, crime, family dysfunction, substance abuse, child abuse and poor support networks are prevalent and additional threats to the well-being of the developing child.

Stress on families and caregivers is particularly prevalent under these conditions, and recent epidemiological data point to the scale of extreme acute and chronic stress experienced by so many of our children and their families:

- 58% of children under 9 years of age live in households with a monthly per capita income of less than R604 – the accepted lower poverty line for South Africa (Berry *et al*, 2013).
- Recent homicide rates for children under 5 are estimated to be 14 per 100 000 for boys and 11.7 per 100 000 for girls (more than double the rates in low-income (6.1) and other middle-income (5.1) countries (Mathews, et. al., 2012).
- Prevalence of Post Traumatic Stress disorder (PTSD) in South African children is estimated at 8% (Kleintjies *et al.*, 2006).
- Intimate partner violence is a recognised stressor for young children. In South Africa this affects at least 25% of adults over the course of their lifetime. Households in poverty are most affected (Seedat, et. al., 2009).
- 33% of South African parents use a stick or other object to chastise their children. The most common age for this form of discipline is 4 years (Dawes, et. al., 2005).
- Prevalence estimates for child maltreatment are not available in SA, and police figures are not reliable. However, rates are likely to be significant (Richter and Dawes, 2008).
- Of approximately 7 million children under 6 years old in South Africa at least 3 million are likely to have direct biological risk factors for loss of developmental potential (See companion Ilifa paper: Biological risks to child development in the first 1000 days, Donald 2013)

This paper describes how stresses such as those described above, become embedded in the bodies, brains and minds of South African children, with dire social consequences. That said, it is important to note that the impact of poverty is not inevitable. Its effects are mediated by those who care for the child, and the period of the child's development when he or she is particularly sensitive to particular insults.

The paper discusses the manner in which the environment interacts with the young child's genes to shape their expression. Enduring stress to the child during the first 1000 days (from pregnancy to 24 months) is particularly damaging, leaving its mark for life. The critical importance of adequate care in this period, and of interventions that support caregivers is emphasized.

It is a companion piece to that compiled by Donald for Ilifa Labantwana on the Biological Risks to Child Development in the first 1000 days of life.

From nature versus nurture to epigenetic marks

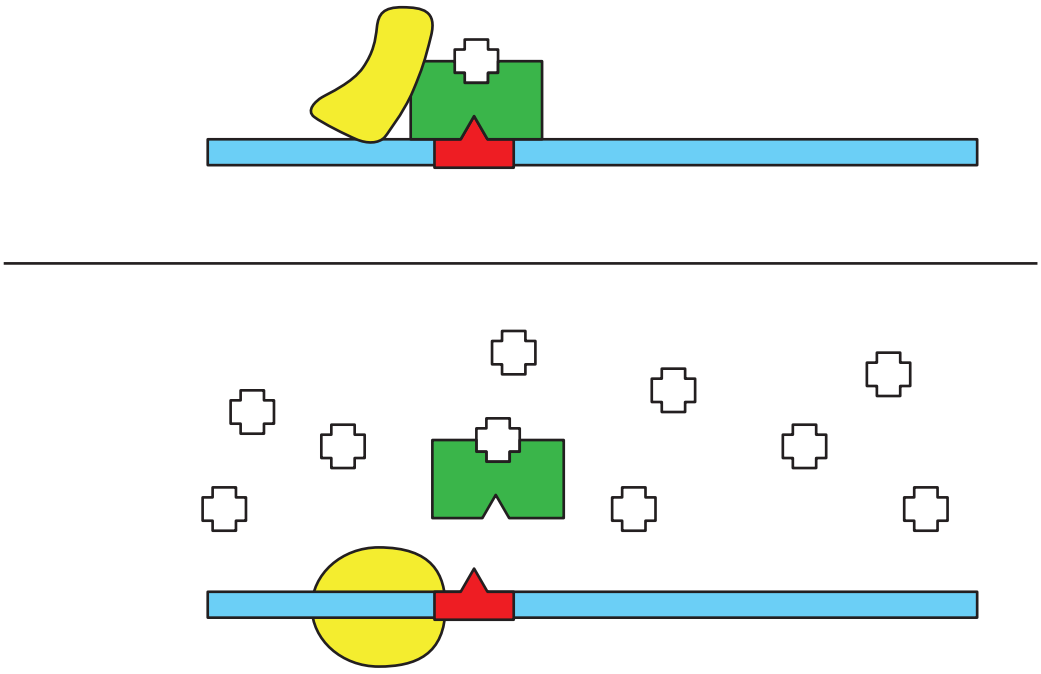
Debate over the relative influences of heredity (*Nature*) and environment (*Nurture*) on human development has been evident since the 19th Century. The story begins with the discovery of the double-helix structure of DNA in 1953 for which James Watson and Francis Crick won the Nobel Prize. DNA – the molecular basis of genes – constitutes the *Nature* side of the debate: DNA is what you inherit from your parents - genetic information honed by evolution over countless millennia. Fewer people know that French scientists Francis Jacob and Jacques Monod won the Nobel Prize in 1969 for discovering that DNA is regulated by the environment, the *Nurture* side of the debate.

It has become *clear that Nature and Nurture, genes and environment, are not only of equal importance, but form an inseparable whole*. As depicted in Figure 1, genes can do nothing alone, something in the environment must tell DNA when and what to do. *Nature* versus *Nurture* turns out to be Nature *and* Nurture

Further research on the bacteria *E. coli* helps us to understand the way environment regulates the expression of genes. Jacob and Monod investigated how the gene coding for the enzyme responsible for digesting sugar is regulated[1] (Figure 1). The yellow shape in figure 1 represents a protein called the *initiator* responsible for initiating gene expression and the green shape is another protein called the *repressor*. The grey bar is the DNA. The upper panel of figure 1 shows how the *initiator* (yellow) binds to the DNA but so does the *repressor* (green) preventing the *initiator* from initiating gene expression (i.e. making the enzyme). However, when there is sugar in the environment (white + shapes, lower panel), it binds to the *repressor* causing it to release its grip on the DNA, thereby opening the way for gene expression (arrow). The initiator is now free to read off the information encoded in DNA needed to make the enzyme (not shown) which then digests the sugar. As soon as all the sugar is digested there is none left to bind to the *repressor* which then once again binds to the DNA preventing any further gene expression. Allowing the initiator to continue making enzymes in the absence of sugar would be futile and wasteful of the cell's limited resources.

1 http://en.wikipedia.org/wiki/Lac_operon

FIGURE 1. Gene regulation by the environment. See text for details.



(Source: This figure is modified by the author from of an online figure: http://en.wikipedia.org/wiki/lac_operon)

Scientists soon discovered the same principles at work in mammalian cells, including humans. In fact environmental regulation is the rule – since all cells in the body contain identical genetic material, and some genes are active in, for example, white blood cells while other genes are active in liver cells, environmental regulation is the only way these differences can come about. Liver and white blood cells occupy different chemical *environments* (*Nurture*) within the developing embryo, and these chemical differences are what make them different, nothing else.

It has recently become clear that the same gene-environment regulatory interactions described above apply to the development and expression of intelligence, emotions and behaviour – which has profound social policy implications. This is simply because genes within brain cells – neurons – are, like all cells, *environmentally regulated*.

What has recently become so compelling however, are the *enduring ways whereby neuronal genes are regulated by the social environment* during early childhood, with dramatic consequences for the makings of intelligence, emotions, behaviour and health throughout the lifespan.

Once-off environmental regulation

Many human genes are, like the *E. coli* gene described above, switched on and off according to changes in the local chemical environment of the cell. However, some human genes are set *neither fully on nor fully off but somewhere in between.*

During sensitive periods in early life, genes may be set *in a* ***once-off*** *permanent* manner as a function of the child's environment. *Critically, this setting remains unchanged for life.* This is achieved by signals from the environment permanently adding small molecules called ***epigenetic marks*** onto the DNA. Like the *E. coli repressor*, epigenetic marks block gene expression but unlike the bacterial *repressor*, epigenetic marks block gene expression only *partially*. Specifically, the *number* of epigenetic marks added to a gene determines the setting for that gene – the more marks, the more gene expression is blocked.

In sum, the permanent nature of epigenetic marks during sensitive early periods, means that gene expression is set at a particular level for life. Once a sensitive period has passed, a gene is highly resistant to environmental influence.

This combination of early sensitivity followed by later resistance is called '*canalisation'*. It is as if development, after being steered one way or another during a sensitive period, becomes confined to a narrow steep-sided canyon or canal. After branching one way or another, it is extremely difficult or even impossible for environmental factors to shift development from one canal into another. There is usually no turning back after this has occurred (but see Remediation section below).

In the brain hundreds, if not thousands, of genes are once-off regulated after birth reflecting the fact that the brain more than any other organ is not fully developed at birth but undergoes significant development during early childhood. Consequently, a child's early environment, both prenatal and postnatal, has a profound canalising impact on the structure and function of its brain.

What about the role of nature? Gene-environment interactions

Are differences between individuals solely attributable to *Nurture*, to differences in the environment during sensitive periods? Certainly not - differences in the information encoded *within* DNA (i.e. genetic differences) influence the extent to which the environment can add epigenetic marks to a particular gene. Thus under *identical* environmental conditions, different amounts of epigenetic marking will occur and consequently gene expression levels will differ. *Ultimately, inherited genetic information and environmentally acquired epigenetic information are where Nature and Nurture physically meet.* This is what is meant by gene-environment interactions.

In sum, neither genes nor environment express themselves directly in human development. All development is a product of gene-environment interactions. Development is the product of thousands of gene-environment interactions which themselves interact in myriad ways. It is nevertheless possible to tease out the ways whereby epigenetic marking of individual genes canalises development in particular respects. Moreover, it is possible to do this for genes influencing health, cognitive, emotional and behavioural developmental outcomes. Indeed, one such gene-environment interaction wields a pervasive influence over all of these outcomes by virtue of its role in the stress response.

The stress response

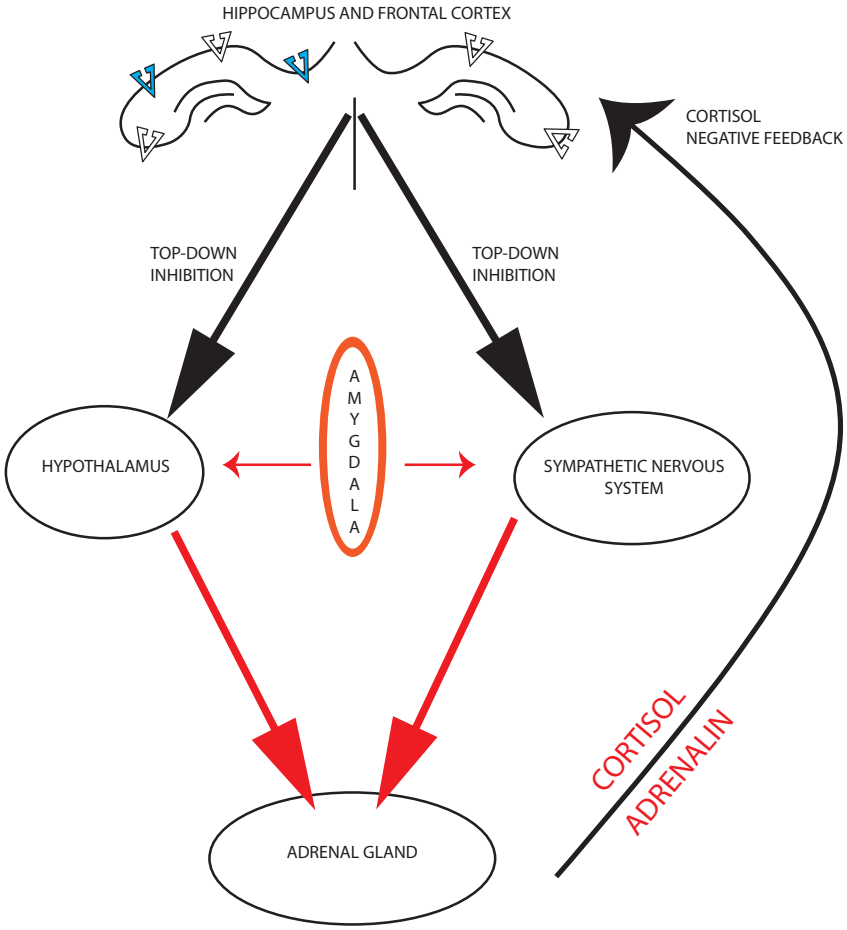
We have noted that stress (particularly of an enduring nature) during early sensitive periods is not conducive to healthy development. Why is this, and how does the brain process stress?

The stress response denotes physiological and psychological changes which occur in response to a stressor and comprises of two systems: the sympathetic nervous system (SNS) and the hypothalamus-adrenal (HA) axis (Figure 2). The former causes the release of adrenalin from the adrenal glands and responds rapidly, preparing the body (increased heart rate, blood pressure, respiration) and focusing the mind in order to respond to the stressor appropriately: if the stressor poses an imminent threat, the SNS will trigger a fight or flight response (FF)

accompanied by feelings and sensations of panic. If the stressor does not pose an imminent threat, the SNS will keep the body in a state of anxious readiness that concentrates cognition towards assessing the overall situation in order to predict what might happen next and what is the best thing to do about it.

If the stressor passes, the SNS response will die down, bodily functions will return to normal and the mind will relax. But if the stressor persists, the HA axis begins to kick in resulting in the release of cortisol, also from the adrenal glands. The HA axis stress response serves to provide the SNS response with energy (increases blood glucose levels) needed to sustain increased heart rate, blood pressure, respiration plus any strenuous physical activity associated with a potential fight or flee response. Just as for the SNS, once a stressor passes, the HA axis will be switched off and blood glucose levels will return to normal.

FIGURE 2: The brain with cortex (hippocampus + frontal cortex), subcortex (hypothalamus, amygdala and sympathetic nervous system) and adrenal glands.



(Source: Upper part of this figure modified from Figure 1 in Meaney and Szyf, 2005)

The stress response and gene environment interactions

So what has the stress response got to do with gene-environment interactions, epigenetic marks and once-off canalisation in early childhood? The story begins with the proverbial lab rat. It was discovered that rat mothers can be divided into those who lick and groom (LG) their newborn pups more (high LG group) and those who don't lick and groom them as much (low LG group). Pups raised by high LG mothers grow up to become resilient to stress (normal HA stress response), whereas pups raised by low LG mothers exhibit an exaggerated HA stress response and are susceptible to the toxic effects of stress. *Crucially, this is true irrespective of who is the biological mother.* In other words pups born to a high LG mother but raised by a low LG mother will develop an exaggerated HA stress response and vice-versa.

This suggests that environment (high or low LG) rather than genes influences how the HA system behaves and this is exactly what has been found. As shown in Figure 2, the HA axis comprises the hypothalamus, a subcortical structure, which stimulates the adrenal gland to release cortisol. The SNS is also a subcortical structure which stimulates the adrenal gland to secrete adrenalin. In the absence of stress, the hippocampus (which is part of the cerebral cortex) prevents cortisol release

by inhibiting the hypothalamus from stimulating the adrenal gland. Similarly, parts of the prefrontal cortex inhibit the SNS from initiating a stress response via adrenalin release from the adrenal glands. Cortical inhibition of subcortical activity is called top-down control.

In the presence of stress, the amygdala – another subcortical structure and chief threat detector in the brain – sends stimulatory signals to the hypothalamus and SNS which can override hippocampal and prefrontal inhibitory control causing SNS and HA activation which release adrenalin and cortisol into the blood stream. ***Bottom-up control*** is when subcortical amygdala, hypothalamus and SNS activity *override* top-down cortical control causing adrenalin and cortisol release. Whenever this happens, while cortisol does its work around the body increasing blood glucose levels, it also reaches the hippocampus where it binds to cortisol receptors like a key fitting into a lock. Opening this lock boosts the top-down inhibitory powers of the hippocampus on the hypothalamus, thereby switching off the HA axis once again. This is known as negative feedback (Figure 2).

If the number of cortisol receptor locks in the hippocampus is low (as depicted on the right hand side of figure 2), the intensity of negative feedback will be low – there will be more keys than there are locks to open and the hippocampus will be less able to switch the hypothalamus off. Consequently, the cortisol stress response will be abnormally high and abnormally prolonged. ***Now the punch line of this story is that the number of cortisol receptor locks is under environmental control during the first few days from birth.*** Specifically, the intensity of maternal LG during the first 6 days of life regulates the level of gene expression of the cortisol receptor gene in a *once-off* fashion for life. Pups raised by high LG mothers have less epigenetic marks on this gene resulting in more gene expression, which in turn results in more hippocampal locks, more effective cortisol key negative feedback, more top-down inhibition of the hypothalamus and hence more effective termination of the HA stress response. Conversely, pups raised by low LG mothers have more epigenetic marks on this gene resulting in less gene expression, which in turn results in less hippocampal locks, less negative feedback and an exaggerated and prolonged HA stress response. Lastly and most importantly, the amount of LG a pup receives after the 6th day of life has no influence whatsoever on the number epigenetic marks already laid down in the hippocampus. In other words, the HA stress response is once-off epigenetically set - canalised - for life during a very brief and well-defined sensitive period from 0 and 6 days of life (Cameron *et al.* 2005, Jensen & Champagne 2012).

Importantly, exactly the same seems to apply to humans. For example, a study of the hippocampus in adult suicide victims found significantly more epigenetic marks on the cortisol receptor gene and, as would be expected, significantly lower levels of cortisol receptor numbers in individuals with a history of early childhood abuse compared to those without any history of early life abuse (McGowan *et al.* 2011). Another study found that early adversity, meaning one or more of parental loss, childhood maltreatment and inadequate parental care, was associated with increased epigenetic marking of the cortisol receptor gene which was in turn associated with weakened negative feedback of the HA axis. Other studies have found increased epigenetic marking of the cortisol receptor gene in children exposed to (i) maltreatment and reduced nurturing, (ii) maternal anxiety and depression in pregnancy (the latter being associated with increased stress reactivity at 3 months of age), and in (iii) 10-19 year olds whose mothers experienced intimate partner violence during pregnancy. Additionally, epidemiological studies have found differences in epigenetic marks on hundreds of genes in individuals belonging to the lowest SES strata, irrespective of adulthood SES; as well as in adult suicide victims who experienced severe childhood adversity including abuse.

Self-regulation: keeping or losing your head

In all mammals, including humans, early adversity is associated with greater epigenetic marking of not only the cortisol receptor gene but many genes across the entire genome. A great many of these other genes are known to be involved in top-down regulation of the stress response. Consequently, early life adversity can bias the brain towards less efficient top-down inhibitory control making spontaneous bottom-up activity more likely.

In conditions of enduring poverty, and challenges such as exposure to violence and low levels of social support, the psychological resources of mothers (and other caregivers) are sapped, and this makes it particularly challenging for them to provide warm and affectionate care and buffer children from these adversities (although many manage to do so despite the odds). This point is revisited later in the paper.

The value of top-down regulation lies in the ability of the cortex to inhibit bottom-up emotional activity and instead integrate a wide range of information in order to make far more sophisticated assessments of what's going on and what to do about it than the subcortex can. The cortex sees the bigger picture. The value of the subcortex is to override top-down cortical control whenever the situation is such that there is no time to ponder different options and one or more of a limited number of automatic stereotyped FF stress or appetitive responses are urgently needed[2] (Blair 2010, Blair & Raver 2012).

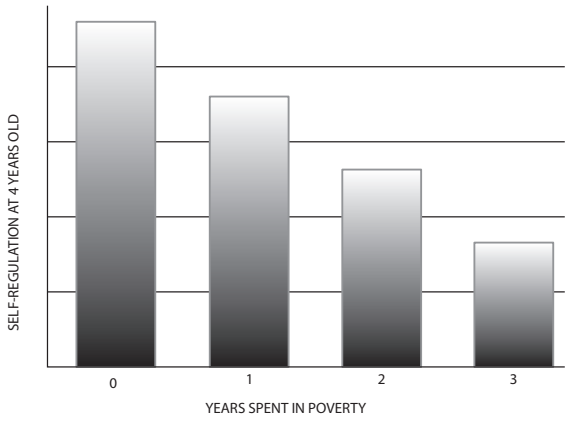
[2] Bottom-up activity encompasses much more than just the FF stress response and also includes appetitive reward-seeking motivations and other emotionally positive and negative states of mind.

In general, top-down cortical regulation of the subcortex is voluntary, effortful and relatively slow. In contrast, bottom-up subcortical activity is involuntary, effortless and instantaneous. Because top-down regulation is generally voluntary and often challenging it is also called self-regulation or 'effortful control' and a healthy balance between top-down and bottom-up activity is important for personal and social wellbeing. A healthy balance means knowing when to keep your head (as opposed to losing it) and when to let go.

Unsurprisingly, self-regulation has a profound influence over lifetime achievement and physical/mental health. Children with poor self-regulation capacities at ages 3, 5, 7, 9 and 11 years old have at 32 years of age significantly higher rates of substance dependence, criminality, financial problems and single parenthood; and significantly lower income, financial planning skills, socioeconomic status and physical health. Although these relationships hold irrespective of childhood SES, lower childhood SES was correlated with poorer self-regulation. Nevertheless, in many cases poor childhood self-regulation was a stronger predictor of poor outcomes in adulthood than was SES status or IQ (Moffitt *et al.* 2011).

Although this study (and others to be described below) reports relationships between SES, adult achievements and self-regulation measured between 3 and 11 years of age, this does not mean that self-regulation capacities are necessarily, largely or only shaped during this period of childhood. As shown in figure 3, self-regulation is strongly related to poverty during the earliest postnatal years and diminishes further with each additional year spent in poverty.

FIGURE 3. Self-regulation as measured at 48 months (y axis) decreases sharply as number of years spent in poverty increases (x axis).



(Source: Blair and Raver, 2012)

Whence self-regulation?

But where does self-regulation come from? Starting from birth an infant has very limited powers of self-regulation because the immature cortex cannot integrate complex information or assert top-down inhibition. As already described for the HA axis in rats and humans, the acquisition of top-down control is highly sensitive to parental investment in early life. In both species the quality of early parental care literally sculpts the self-regulatory powers of the maturing cortex via epigenetic marks that determine the density of cortisol receptors on hippocampal cells and the same applies to the expression of many other genes in the brain.

Numerous human neuroimaging studies support this. The prefrontal cortex of 24 year olds from lower childhood SES backgrounds was less able to inhibit amygdala activity during an effortful negative emotion regulation experiment independent of adult SES. Moreover, chronic childhood stressor levels mediated this effect. Similarly, in a sample of 60 children (mean age 11.4 years), lower SES correlated with smaller hippocampal and larger amygdala volumes. Another study found that lower childhood SES predicted smaller hippocampal volumes 50 years later. Lastly, a further study found that parental SES predicted cognitive function and prefrontal cortex activity in 8-12 year old children and that this relationship was mediated by cortisol stress response reactivity and complexity of the child's home language environment.

Because a baby is born with a well-developed subcortex, any distress it feels triggers a powerful stress response which it has no means to curtail – there are no or very few cortisol receptors in the hippocampus as yet and no cognitive powers of self-regulation. Instead, it relies on its mother to comfort it, to regulate its feelings. Even if the mother's efforts to comfort the baby are not entirely or immediately successful, her mere unconditional presence and deeply caring attention results, as in the case of high LG rat mothers, in fewer epigenetic marks on the cortisol receptor gene and other genes important for top-down control. ***And this is how strong powers of top-down self-regulation are acquired – from the environment which for infants is predominantly the mother/caregiver***. Importantly, strong self-regulation does not mean suppression of all emotional responses. Non-judgemental tolerant and empathic parenting allows an infant to first safely express, and later verbalise and thereby self-regulate subcortically generated distress or excitement such as hurt, anxiety, fear, anger and desires.

In sum, the mother is said to *buffer* the infant's subcortical stress response from overwhelming and damaging the infant's body and mind. Maternal buffering also refers to the mother's role in protecting the infant from external stressors so as not to activate the infant's stress response in the first place.

Although the term "mother" is generally used it is important to acknowledge that the primary caregiver of a great many South African children is not their biological mother. Only 39% are raised by their biological mother, 33% by both biological parents, 24% by neither biological parent and 4% by their biological father. Non-biological parent caregivers are frequently grandmothers and other kin.

Maternal mediation hypothesis

There is good evidence to support the idea that once-off calibration of the stress response according to the quality of maternal care early in life serves to prepare offspring for the kind of environment likely to be encountered as an adult. A relatively safe bountiful environment characterized by low levels of maternal stress mothers devote relatively more resources to caring for their offspring. As a consequence these offspring develop strong top-down regulation of the stress response. Conversely, caregivers inhabiting a relatively unsafe impoverished stressful environment devote fewer resources to maternal care resulting in weaker top-down regulation of the stress response. This is appropriate because impoverished environments are associated with nutritional deprivation, violence and infection and weaker top-down control of the stress response provides enhanced protection against all three conditions. For example, weaker top-down control promotes anxiety, fear, caution, avoidance, defensive hostility and mobilization of stored energy – all optimal responses in a high-risk resource-scarce environment.

In this way, information about the qualities of the external environment that offspring are soon to enter, are forecast to offspring via their caregiver's behavior. Extensive evidence in animals and humans supports this idea known as the *maternal mediation hypothesis* (Cameron *et al*. 2005, Jensen & Champagne 2012). For example, in the context of poverty and its stressors, lower education, meagre income, multiple children, lack of social support and single parenthood all correlate with harsher parenting styles. The risk of neglect and abuse is also raised.

In line with once-off setting of the stress response in early life, adult victims of child abuse show increased HA and SNS responses to stress. Poverty is also associated with a high incidence of depression and anxiety disorders in mothers, and depressed and anxious mothers are less able to feel positive towards their baby (Wachs and Rahman, 2013). This results in poor maternal-infant bonding which in turn correlates with increased bottom-up SNS and HA stress responses in offspring. There is also animal and human evidence that mothers invest fewer resources in many offspring under adverse conditions and invest more resources in fewer offspring in benign conditions.

Toxic stress

A benign environment regulates for high parental investment which in turn engenders strong top-down self-regulation, yielding a child and ultimately an adult who is able to cope with most stressful situations life has to offer such as social tensions, physical challenges, and school or job-related stress. Coping here means that under stress top-down regulation is maintained so that effective rational responses can be made. An adverse stressful environment on the other hand regulates for low parental investment which in turn results in a child prone to respond to stressful situations with adaptive bottom-up responses that can nevertheless be physically, cognitively, emotionally and socially damaging[3].

Stress that can be coped with is known as *manageable stress* and stress that cannot be coped with, or can only be coped with at a significant cost, is called *toxic stress*. Toxic stress results in exaggerated, repeated, prolonged or chronic bottom-up activation of the HA and SNS axes which is physically and psychologically harmful in the longer term, including increased risk for a wide range of adult-onset illness, for example, autoimmune disorders, substance abuse, and various cardiovascular conditions. Psychologically, it is associated with increased risk for depression, anxiety, substance addiction, poor social skills, suicidal behaviour and suicide. Among children increased incidence of externalising behaviours, teenage pregnancy, conduct disorders and delinquency are evident (Taylor *et al*. 2011).

It is now time to put all these pieces together to explain the toxic effects of poverty on South African children. Infants born into poverty receive less caregiver investment – less buffering - and therefore develop weaker top-down powers of self-regulation and greater bottom-up stress reactivity and emotional impulsivity. Because these contrasting trajectories are strongly canalised – deeply embedded in brain circuitry -whenever stress is later encountered, the probability of an exaggerated bottom-up stress response is higher than for infants raised in more benign nurturing buffered conditions who develop

[3] The picture is actually more complex with genetic factors interacting with environment such that not all individuals who experience compromised parental care develop a stronger bottom-up than top-down mode of brain function and weaker self-regulation.

stronger top-down powers and less impulsive reactive bottom-up emotional tendencies (Blair 2010, Blair & Raver 2012). Thus the same stressor will impact more negatively - more anxiety, fear, panic, aggression and more cortisol and adrenalin release – in the former case. For this reason, children raised in poverty are more susceptible to toxic stress – more liable to not cope psychologically and more likely to suffer physical organ damage and mental illness – than their more affluent counterparts (Taylor *et al*. 2011).

Importantly, as most of the previous examples illustrate, the negative consequences of limited caregiver investment *do not always manifest in frank disability or disease*. Instead, the impact of toxic stress is largely insidious, subtly undermining capabilities such as self-regulation, executive function, linguistic complexity, social skills, all of which are critical in order to compete in the marketplace of life. Moreover, children do not have to be beaten or sexually abused to manifest HA and SNS hyper-responsiveness or its long term sequelae. More subtle forms of limited parental investment can have equally toxic impacts. For example, chronic maternal depression – where normal dyadic emotional interplay fails because depressed mothers are unable to authentically engage (e.g. delight) in the caregiving experience – has well established negative impacts on self-regulation and socialising abilities during infancy and in later life. Similarly, moderate levels of pre- and postnatal anxiety increase the risk of conduct disorder in adolescence and the complexity of language in the home correlates with self-regulatory outcomes.

From maternal mediation to vicious and virtuous cycles

The central mediating role of parental care makes it important to not only focus on biological embedding of environment with respect to brain development and self-regulation, but also with respect to parental care itself. Evidence from humans and non-human primates shows that children who experience maltreatment or even mild to moderately compromised maternal buffering (that is nonetheless within the "normal" range) show disturbed HA activity throughout life. Additionally, mothers who as children experienced compromised parental care or maltreatment exhibit lower maternal sensitivity towards their own offspring. Importantly, human evidence shows that this relationship between early life experience and maternal caregiving qualities is mediated by exaggerated HA activity and weakened top-down executive function, as opposed to via a purely psychosocial pathway (Gonzalez *et al*. 2012). Indeed, the emerging biodevelopmental model is built upon a very wide range of human and animal evidence highlighting the importance of multiple causal biological pathways from environment to developmental outcomes. These pathways encompass the biological embedding of environmental conditions in multiple systems (which includes psychological and behavioural elements) as a function of gene x environment interactions (Shonkoff 2010).

The shape and impact of these pathways are sculpted in a once-off way during early development when environmental influences, as mediated by parental care, are most deeply embedded in offspring biology. Just as high or low maternal LG during the first few days of life influences epigenetic marking of the cortisol receptor gene which in turn determines the number of cortisol receptor locks on hippocampal cells, female rat pups raised by low LG mothers become low LG mothers themselves via once-off epigenetic marking of genes in the hypothalamus responsible for the expression of caregiving behaviours (Jensen and Champagne 2012).

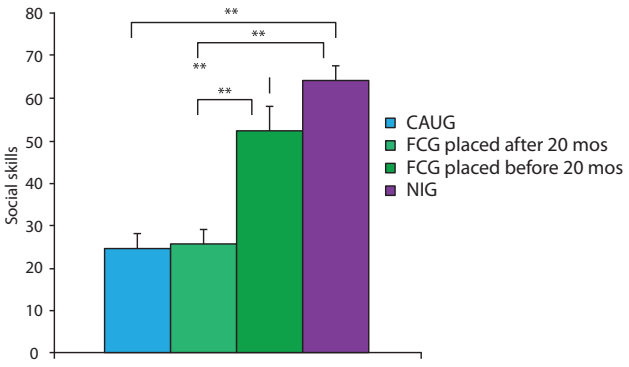
Taken together, common patterns of transmission of maternal caregiving behavior from mothers to daughters in animals and humans, together with evidence of common biological pathways, provides new insights into the "cycle of poverty". In sum, a *vicious* toxic stress cycle is set in motion whereby an adverse poverty environment, as mediated by parental caregiving behaviours, becomes embedded in offspring during early development via once-off epigenetic canalisation of the HA axis and hypothalamic reproductive functions, resulting in both compromised top-down self-regulation and compromised maternal care. In contrast, adequate maternal buffering as is more likely to occur in a less stressful environment engenders resilient offspring with strong top-down self-regulatory powers and when grown up, enhanced maternal sensitivity. Importantly, adequate maternal buffering which makes an earlier stressor more manageable *also renders a later more severe stressor (one that would otherwise evoke toxic stress) more manageable*. Such a "success breeds success" chain reaction within one generation is amplified over ensuing generations via the same once-off maternal behaviour-to-epigenetic embedding pathways described above. But in this case a *virtuous* as opposed to *vicious* trans-generational cycle is set in motion. Unlike susceptible offspring rendered vulnerable by early exposure to toxic stress, resilient offspring are able to shake off the stresses of life and cope or even thrive without developing physical, psychological or social pathologies. Clearly such maternal behaviour-to-epigenetic transmission of cognitive, emotional and behavioural self-regulatory and caregiving traits from one generation to the next through the neurodevelopmental embedding of early life experience has implications for research, policy and practice aimed at breaking the vicious cycle of poverty.

Remediation

It is important to point out that the exact timing and duration of sensitive periods in humans is not known. Indeed, it is likely there is no exact timing or duration for all humans as there is in rats[4]. The term once-off should therefore not be taken to mean that environmental conditions inscribe genes with indelible epigenetic marks in a matter of minutes, hours, days or weeks but rather that permanent epigenetic marking of genes occurs across a series of often overlapping sensitive periods that is relatively short in relation to the overall lifespan. All we know at this stage is that early life conditions, especially caregiver qualities, do have lasting once-off consequences on both epigenetic marks and the development of neural systems underlying powers of top-down self-regulation in humans.

Nevertheless, although the trajectories of some fundamentally important aspects of brain development may be canalized in a once-off fashion early in life, the development of the brain as a whole is by no means forever set in stone. Studies of institutionalized Romanian children exposed to severe early emotional deprivation, who were subsequently adopted into caring homes at differing ages provide invaluable insights into the critical importance of timing for developmental remediation and recovery. In addition to the impact of age of adoption on social skills shown in figure 4, studies have shown increased behavioural problems and decreased IQ after adoption at 8 but not 4 months old. Other studies have found decreased cortical gray matter, disorganized cortical brain function and HA axis disturbances in Romanian children adopted at later versus earlier ages.

FIGURE 4. Social skills at 8 years of age in Romanian children placed in severely deprived institutional conditions soon after birth and later adopted into nurturing foster families.



(Source: Almas *et al.* 2012)

In Figure 4, the blue bar refers to children who remained in Romanian institutions; the pale green bar is children placed into foster care after 20 months of age; the dark green bar is children placed into foster care before 20 months of age, and the purple bar is Canadian children who had never been institutionalised.

These studies underscore the critical importance of sensitive periods in human development across biological, cognitive, affective, social and behavioural domains as well as the potential for timeous remedial intervention. Far more detailed study of the potential (and temporal dynamics) for modifying the effects of early canalisation in humans is needed, especially in non-clinical community settings where environmental conditions are not as extremely adverse as for the Romanian orphans and early canalisation may be even more amenable to remediation. It is only through empirical research that a detailed and nuanced understanding of the malleability of developmental trajectories already constrained by early gene x environment and neurodevelopmental canalisation can emerge.

It is also important to understand that while an instance of once-off canalisation at the epigenetic level may be irreversible its effects on brain function may still be modifiable through higher level processes (e.g. cognitive behavioural therapy can help to partially modify – re-canalise or at least consciously regulate in a top-down manner - cognitive, mood or behavioural habits already embedded, canalised in neural tissue). Similarly, the process of fear extinction – extinguishing a conditioned reaction to an adverse stimulus – does not entail undoing, reversing, the neural connections mediating that conditioned reaction. Instead, although these connections remain intact, fear extinction is mediated by a new connection originating elsewhere in the brain that top-down inhibits the original connection. Equally, a massive environmental 'push' (e.g. a highly traumatic event) can 'flip' a highly canalised normal brain into a highly canalised pathological brain as occurs in post-traumatic stress disorder.

Summary

This contribution has described the basic mechanisms whereby genes and early environmental conditions conspire to set the long term developmental trajectories of neurobiological systems underlying major cognitive, emotional, social and behavioural function. Healthy nuanced well-balanced integration of these systems - such as occurs in a safe, high-investment, well-buffered, early nurturing environment - underlies optimal functioning of core biopsychosocial capacities such as self-regulation that are so critical for intrapersonal and interpersonal harmony, success and happiness in life. Only very recently has interdisciplinary neuroscience begun to reveal

4 Developmentalists have ascertained approximate ages for acquiring particular motor, language, cognitive and self-regulatory skills but these are nowhere as well defined as the sensitive period for epigenetic marking of the cortisol receptor gene in rats is.

and characterise the stress of chronic poverty as a major environmental toxin that becomes embedded in the biological fabric of bodies, brains and minds in ways that cripple healthy development of such capacities. Being embedded at the most fundamental levels of gene-environment biology, these contrasting trajectories gain intergenerational momentum as vicious or virtuous cycles, thereby reinforcing socioeconomic inequity. For children living in chronic poverty in South Africa toxic stress as here understood is a newly recognised pandemic that must be addressed.

Conclusion

Do caregiver-child relationships matter more than poverty?

Remarkably, given everything described above, toxic stress is not directly caused by poverty (Yoshikawa *et al*. 2012). The relationship is instead entirely mediated by the quality of parental care: controlling for parental factors completely cancels out the effect of poverty (Cameron *et al*. 2005). This can be taken as a potent argument to vigorously scale up interventions targeting support for primary caregivers. However, the emerging interdisciplinary understanding of how Nature and Nurture interact to shape human cognitive, emotional and social development challenges societies with a biological, psychological, social, economic, political and ultimately moral greater truth:

"Ultimately, we will need to contend with the reality that neural development, function and health are defined by social and economic influences, and that the success of interventions that ignore such forces will be seriously limited." (Cameron et al. 2005)

Take-home messages

1. Recent insights into how environmental adversity becomes deeply and to a large extent irreversibly embedded in biology during early human development constitutes a paradigm shift of epic proportions.
2. These advances are being successfully used in many countries to persuade policy makers to allocate greater resources (of all kinds) towards protecting and nurturing early human development. In some cases, governments have taken the initiative themselves to reach out for the expertise needed to reconfigure early development policy and practice.
3. Poverty is, via diminished caregiver investment and other factors, toxic: Societies with the largest income differences between the top and bottom 20% have the worst childhood outcomes.
4. Epigenetics provides new insights into the transgenerational transmission of environmental effects that sharpen our understanding of the cycle of poverty and argue for long term social policy perspectives.
5. Gene-environment interactions occur over extended sensitive periods during early childhood. However, overall the window of sensitivity diminishes extremely rapidly, effectively reaching adult levels by the age of 6-7 years old. Although brain development continues for at least the first 22 years of life, and although adolescence presents a new window of heightened sensitivity, early prevention and remediation interventions will always be most effective and most cost-effective.

References and Additional Resources

Freely Available Information

The following sites provide free access to extensive literature about understanding and addressing toxic stress in childhood:

Shonkoff, J. P. and Phillips, D. A. (Eds) (2000). From Neurons to Neighborhoods: The Science of Early Childhood Development Washington, DC: National Academic Press. http//www.nap.edu/openbook.

Bernard van Leer Foundation www.bernardvanleer.org http://www.bernardvanleer.org/English/Home/Publications.html#.UotnpZUyOfQ

Centre on the Developing Child, Harvard University http://developingchild.harvard.edu

How Brains are Built: The Core Story of Brain Development Alberta Family Wellness Initiative (AFWI) http://www.albertafamilywellness.org, http://www.albertafamilywellness.org/resources/video/how-brains-are-built-core-story-brain-development

References

Almas N *et al*. (2012) Effects of early intervention and the moderating effects of brain activity on institutionalized children's social skills at age 8. *Proceedings of the National Academy Sciences*, 109 (Suppl. 2), 17228–17231.

Berry L *et al*. (2013) Getting the basics right. An essential package of services and support for ECD. In Berry L, Biersteker L, Dawes A, Lake L & Smith C (Eds.) *South African Child Gauge 2013* (pp. 26-33). Cape Town: Children's Institute, University of Cape Town.

Blair C. (2010). Stress and the development of self-regulation in context. *Child Development Perspectives*, 4(3), 181-188.

Cameron, N.M. et. al. (2005). The programming of individual differences in defensive responses and reproductive strategies in the rat through variations in maternal care. *Neuroscience and Biobehavioral Reviews,* 29, 843-865.

Clancy, B. & Raver, C.C. (2012). Individual Development and Evolution: Experiential Canalization of Self-Regulation. *Developmental Psychology*, 2012, 48(3), 647–657.

Dawes A, de Sas Kropiwnicki, Z., Kafaar, Z. & Richter, L. (2005) Corporal Punishment. *Article 19*, 1(2), 1-3.

Gonzalez, A. et. al. (2012) Maternal Early Life Experiences and Parenting: The Mediating Role of Cortisol and Executive Function. *Journal of the American Academay of Child and Adolescent. Psychiatry*, 51(7), 673–682.

Jensen, C.L. & Champagne, F.A. (2012). Epigenetic and Neurodevelopmental Perspectives on Variation in Parenting Behavior. *Parent Sci Pract*. 2012 April 1; 12(2-3): 202–211. doi:10.1080/15295192.2012.683358.

Kleintjies, S. et. al. (2006) The prevalence of mental disorders among children, adolescents and adults in the Western Cape, South Africa. *South African Psychiatry Review 9*: 157-160.

Mathews, S., et. al. (2012) Child Homicide Patterns in South Africa: Is There a Link to Child Abuse? *Research Brief, South African Medical Research Council* August.

McGowan, P.O. et. al. (2009) Epigenetic regulation of the glucocorticoid receptor in human brain associates with childhood abuse. *Nature Neuroscience*, *12*(3), 342–8. doi:10.1038/nn.2270.

McLoyd, V. (1998). Socio-economic disadvantage and child development. *American Psychologist*, 53, 185-204.

Meaney, M.J., & Szyf, M. (2005). Maternal care as a model for experience-dependent chromatin plasticity? Trends in Neurosciences, 28(9), 456–463.

Moffitt, T.E. *et al*. (2011) A gradient of childhood self-control predicts health, wealth, and public safety. *Proceedings National Academy Sciences*,108(7), 2693–2698.

Richter, L. & Dawes, A. (2008). Child abuse in South Africa: Rights and wrongs. *Child Abuse Review*, 17(2), 79-93.

Seedat, M. et. al. (2009) Health in South Africa 5. Violence and injuries in South Africa: prioritising an agenda for prevention. *The Lancet*, 374, 1011-1022.

Shonkoff, J.P. (2010). Building a New Biodevelopmental Framework to Guide the Future of Early Childhood Policy. *Child Development,* 81 (1), 357–367.

Taylor, S.E. et. al. (2011) Early adversity and adult health outcomes. *Development and Psychopathology*, 23, 939-954.

Wachs, T. & Rahman, A. (2013). The nature and impact of risk and protective influences on children's development in low and middle income countries. In: Rebello-Britto, P., Engle, P. and Super, C. (eds.) *Handbook of Early childhood Development Research and its Impact on Global Policy* (pp.85-160). New York: Oxford.

Yoshikawa, H. et, al. (2012). The Effects of Poverty on the Mental, Emotional, and Behavioral Health of Children and Youth Implications for Prevention. *American Psychologist,* Vol. 67, No. 4, 272–284 DOI: 10.1037/a0028015.