RESEARCH SUMMARY

STRESS PHYSIOLOGY IN EARLY CHILD DEVELOPMENT

Scientists now understand that the way our brains react to stress is driven by interactions between hormones produced by the hypothalamus, the pituitary and the adrenal glands. This system is known as the hypothalamus-pituitary-adrenal or HPA axis. Two papers, published in 2013, review research into the HPA axis and the stress response in childhood; these show that children are at high risk during the early years and suggest how research into the physiology of stress might help develop interventions to prevent some of the potential effects of adverse care during early childhood.

Paper 1 of 2

Stress physiology and developmental psychopathology: past, present and future (2013)
Doom, J.R. and Gunnar, M.R.
Development and Psychopathology 25, 1359-1373

The past twenty-five years have seen immense strides in our understanding of how mammalian, and particularly human, brains react to stressful situations. By 1989, studies in rodents had shown that pups separated from their mothers for long periods show hormonal response patterns that are similar to those of humans with depression, but methods had not been developed for measuring this response in children. The breakthrough came when researchers realised that the "stress hormone" cortisol can be measured in saliva, which can be obtained very easily even from very young children.

Since the late 1980s we have accumulated an enormous amount of information about the anatomy and physiology of the stress response, and the network of interactions both within and outside the key hypothalamus-pituitary-adrenal (HPA) axis that are involved in regulating it. Briefly, stressful situations trigger the release of a chemical called corticotrophin-releasing hormone (CRH) both from the hypothalamus and from outside the HPA axis. This causes a complex series of responses that have been described overall as "a neuro-symphony of stress" which lead to the release of cortisol and other stress hormones from the adrenal glands near the kidneys. Many other chemicals can be involved in the stress response, and these depend on the duration and nature of the stress, the age and particularly the developmental stage of the individual concerned, and genetic factors. This can explain why individuals differ so greatly in their response to, and their ability to recover from, severe stresses.

Throughout the last 25 years there has been great interest in the ways in which stresses during early life affect the development of humans and other mammals. We now know that this occurs partly, at least, through chemical modifications of DNA that lead to changes in the way that genes are expressed, altering protein production and thus physiology and behaviour. One of the genes regulated by these so-called epigenetic modifications to its DNA in response to stress is the glucocorticoid receptor (GR), which binds cortisol. Experiments in rats showed that pups that experienced poor maternal care showed epigenetic changes to the DNA of their GR, less GR protein expressed in the hippocampus, and poor regulation of the HPA axis. Comparable results have been seen in humans: the brains of suicide victims who had experienced abuse in childhood showed less GR protein expression than "average" brains at

post-mortem, and the same epigenetic changes were observed in cord blood taken from mothers who had been depressed in late pregnancy.

Researchers have also studied the effect of common small differences (or polymorphisms) in genes in the HPA axis and related systems on individuals' response to stress. Particular variants of the genes for the CRH receptor and the serotonin receptor have been linked to depression and to a heightened HPA response to stress respectively. It seems that both the CRH receptor and parts of a complex that regulates the glucocorticoid receptor are involved in controlling emotion, and that some forms of these genes are associated with increased vulnerability to severe childhood stress.

Most experimental studies of stress response in children now depend on measurements of cortisol concentrations in saliva, which have become both more precise and easier to take over the last two decades. It is possible to use this method to capture fluctuations in cortisol levels more or less in real time. Cortisol can also now be measured in hair, showing its accumulation over weeks and months. These methods are complemented by more invasive techniques that can only be used in animal models. Progress has also been made in statistical analysis techniques, which has made precise modelling of patterns of cortisol change over time much easier. As we look forward to the next 25 years we anticipate further advances in our understanding of the coordination of the whole stress response system, and in particular how changes in these systems lead from stressful experiences in early life to psychological difficulties later on, and how this varies between individuals.

We also know that the HPA axis is not fully developed at birth. Therefore, in the first months after birth, even small increases in stress are reflected in large increases in the activity of this axis. This over-reactivity disappears after a few months, particularly in children who have developed attached relationships to their main care-givers. The mechanisms through which attachment protects babies and toddlers against strong biochemical responses to stress are not yet fully understood. It seems likely, however, that the hormone oxytocin, which is involved in social bonding and has been termed the "cuddle hormone", is involved. A fuller understanding of this process will help researchers understand what happens when it goes wrong. Furthermore, the HPA axis also becomes more sensitive during puberty, and this also marks the point where gender differences in patterns of response to stress become apparent.

Animal studies have shown that it is possible to provoke an acute stress response in young mammals by removing them from their mothers. It is of course unethical to reproduce these experiments with human children, but maltreatment, poverty and conflict within families all induce similar stress-related patterns of cortisol release. Many studies have shown milder stress responses in children in daycare, even when that care is supportive. However, individual children differ greatly both in their physiological response to stress and in their later resilience. The factors that influence whether an individual child who has experienced trauma will develop psychiatric symptoms in later life are many and complex, and must include genetics, the timing and duration of the stress, and the child's later experiences. Clinical trials have already shown that it is possible to treat children in foster care in ways that restore their patterns of cortisol release close to those in well-treated children. However, further multi-disciplinary research is needed before we can understand enough about these factors to reliably predict children's stress responses and design interventions that increase their resilience.

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RESEARCH SUMMARY

Paper 2 of 2

Early Adverse Care, Stress Neurobiology, and Prevention Studies: Lessons Learned
Bruce, J., Gunnar, M.R., Pears, K.C. and Fisher, P.A. (2013).
Prevention Science 14, 247-256

It has long been recognised that children who have experienced very stressful situations, such as abuse and neglect in their early years, often have problems with their social, emotional and even physical development as they grow up. Experiments on non-human mammals first suggested that the link between early stress and later problems was mediated by the stress response and in particular the hypothalamus-pituitary-adrenal (HPA) axis. Therefore, researchers need to take the physiology of the stress response into account when designing interventions to select children thought to be most vulnerable to stress in the long term and to increase their resilience. This, however, is complicated by the physiological complexity of that response.

Many studies have implicated problems with regulating the HPA axis in the development of various mental health problems, ranging from depression to disruptive behaviour in childhood. Elevated cortisol levels have been associated with depression, and reduced levels with post-traumatic stress disorder. Most of these studies, however, have been in adults or older children. It seems that the response of the HPA system changes as children develop, and the relationship between cortisol secretion in young children and their mental health later on is complex and difficult to understand completely. Difficulties in regulating the HPA system in childhood are clearly risk factors for mental disorders later on, but the HPA axis does not tell the whole story.

It is clear that adverse care in early childhood can have a profound and long-lasting effect on the functioning of the HPA axis. Different studies, however, have shown different effects, with both enhanced and reduced diurnal cortisol levels being observed. The duration and type of adverse care experienced, the age of the child, and the length of time between the stress and the measurements all seem to affect the nature of the response. There is also variability in response between children who were affected by similar stresses at similar times, and adverse experiences can be cumulative: children who were exposed to cocaine before birth and who also experienced domestic violence were more likely to show a blunted HPA response than those who were just exposed to cocaine.

These results suggest that measuring HPA activity in disadvantaged children might help determine which of them will be more vulnerable to developing mental health problems in later years and therefore which might benefit most from preventative interventions. Several studies have shown that early adverse care has no long-term adverse consequences in a significant minority of children, and it is likely that these will be those whose cortisol levels are least disrupted. Furthermore, the nature of the disruption to the HPA axis might predict the type of problem experienced: maltreated children with low morning cortisol levels might be at risk for post-traumatic stress disorder, while children with high morning cortisol might be at more risk for depression. There are, however, several questions that must be answered before these measurements can be reliably used to select the most vulnerable children. The measured differences in cortisol levels are usually small, and it is difficult to compare measurements between studies as there are so many variables. Therefore it is likely that multiple measurements of cortisol and other “stress chemicals” will be necessary to predict which children are most at risk.

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Researchers have now become interested also in how readily the HPA system can react to interventions designed to prevent long-term effects of early adverse experiences: that is, how plastic this system can be. Several studies have shown that cortisol levels can be normalised and outcomes improved by the same interventions, at least in the short term. For example, in the US, foster children who received a formal intervention designed to promote consistent parenting strategies and child psychosocial development were found to have more typical diurnal cortisol levels and to show more secure attachment behaviour than those who received standard care. Results from these and similar studies suggest that it might even be possible to use cortisol levels, and other measures of HPA activity, as indicators of effectiveness in randomised controlled trials of interventions designed to prevent long-term adverse effects of poor care.

The fact that some children react more severely to adverse care than others has led to speculation that these children may not so much be more vulnerable as more plastic: that is, they may also be more responsive to psychosocial interventions. Some studies of differential stress response have suggested this, although none of these have been in children who experienced early adverse care. Assuming that additional research in these children can confirm this, it should become possible to identify children both who are least likely to benefit from intervention and those who are most likely, and perhaps develop specific strategies to help each of these groups in different ways.

Jacqueline Bruce and her co-authors cited these results to suggest that an understanding of the physiology of stress will be very helpful in the design of intervention strategies to help maltreated children recover and develop normally. They then described this response, and in particular the role of cortisol and the HPA axis, as explained further in the first summary in this pair in detail. Several points were emphasised as being of particular importance to those who seek to use stress response measures in studies of preventive interventions. These include appropriate methods for collecting samples and measuring cortisol in children: the normal and abnormal patterns of its secretion throughout the day: and the importance of including other methods of measuring the activity of the HPA system. The authors concluded by suggesting that researchers who develop interventions for use in clinical practice would benefit from forming collaborations with experts in the physiology of stress.
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