RESEARCH SUMMARY

Maternal caregiving and DNA methylation in human infants and children: Systematic review

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The relationship between adverse early life experiences and later emotional and behavioural difficulties has been studied by scientists for over twenty years. Many studies in both humans and other mammals have shown that this link arises, at least partly, through so-called 'epigenetic' changes to the genome. Whereas an individual's basic genetic complement – the sequence of DNA bases that makes up his or her genes – is essentially unchanged throughout the lifespan, small chemical changes to those bases can influence how the genes are expressed as functional proteins. One of the commonest of these changes is DNA methylation, in which a tiny chemical group is added to one base, reducing the expression of the gene in which it occurs as the functional protein (known as 'gene silencing'). The pattern of DNA methylation in the genome and thus of gene silencing is exquisitely sensitive to variations in the environment experienced by an individual human or animal.

Rodent studies have conclusively shown that pups whose mothers lick and groom them less frequently have higher DNA methylation in genes involved in stress responses, and also that they respond more intensely to stress in adulthood. Conversely, rats reared by sensitive mothers have both less methylation and a less intense stress response. Similar effects have been observed in humans, suggesting that methylation of several genes linked to emotional responses or behaviour were increased after early adverse experiences. However, these relationships are known to be much more complex in humans, not least because maternal care itself is more complex, involving cognitive skills and emotional sensitivity as well as basic physical nurturing.

Livio Provenzi and his colleagues at the 0-3 Centre for the at-Risk Infant, Bosisio Panini, Lecco, Italy has conducted a systematic review of the published literature concerning the effects of human mothers' care of their infants on both their DNA methylation patterns and their developmental outcomes. Some of the selected studies also included adverse events and attempted to discover the extent to which sensitive maternal care could reduce the expected epigenetic changes.

A total of eleven studies were selected for review; all were published in English and concerned human subjects only. These studies can be classified in several different ways. Eight looked simply at how maternal behaviour could predict either DNA methylation or children's outcomes, and the other three at the interaction of all three

variables. Six were undertaken in the context of adverse early life experiences, whether maternal depression, a natural disaster occurring during the pregnancy, or stress arising from (for example) the infant being admitted to a neonatal unit. Five were prospective studies in which the participants were recruited at the start and followed for a specific length of time, and the rest were retrospective studies in which participants were asked to remember their, or their infants', past experience. Four of these included adults looking back at their own childhoods. In each case, DNA was extracted from cheek cells, blood or saliva and methylation assessed either across the genome or in one or several target genes.

Provenzi and his co-authors summarised the results from all eleven studies, starting with two that explored whether nurturing care could moderate the effect of maternal depression on DNA methylation in their infants. These both focused on infants about 4-5 months old and found that the infants of depressed mothers who were, nevertheless, more sensitive and engaging during play had less methylation of the target stress response genes. Infants whose mothers were less sensitive and responsive showed stronger emotional responses to stress such as that imposed by a 'still face' experiment. In this, the mother is asked to suddenly disengage from her infant and remain motionless and unresponsive for two or three minutes. Another study asked mothers who had been through a natural disaster in pregnancy to remember and assess their responses many years later. Adolescent children of the mothers who appraised their response more negatively and of those whose experiences were objectively assessed as being harsher had less methylation of several genes linked to stress, which increases the expression of those genes leading to heightened stress responses.

Five studies assessed the effect of different types of maternal behaviour on methylation levels in their children without any reference to adverse experiences. The children in these studies ranged in age from infancy to adolescence. Helpful methylation patterns in several genes were found to correlate with breastfeeding duration, responsiveness during play, and the quality of prior parental care as assessed by adolescents. Several studies found that correlations were stronger in girls, and these included one that found that children (both boys and girls) who were assessed as securely attached at 36 months had higher DNA methylation levels four years later. These methylations were at sites across the whole genome, where this would dampen stress responses, and were higher than those whose attachment had been assessed as 'disorganised' at the same age.

The authors of one longitudinal study asked mothers to keep a diary describing everything they did to care for their infants and looked for correlations between the amount of physical nurturing and DNA methylation levels in numerous infant genes. Interestingly, definite correlations between methylation and care were found in genes involved in metabolism and inflammation, but not in those involved in stress responses. Another study asked adolescents to assess their parents' behaviour towards them in childhood and investigated the correlation between those responses and methylation of a gene called tumour necrosis factor (TNF), which is involved in inflammatory responses. These researchers found that TNF was 'silenced' by methylation more in young people who reported more protective parenting, so they

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would be expected to suffer less from inflammatory disorders as those with less protective parenting. In general, these young people were also more likely to describe their health as good.

Provenzi and his colleagues summed up the results of all 11 studies as suggesting both that maternal care can regulate infants' and children's behaviour through epigenetic changes to gene expression, and that it can protect them to some extent from the effects of early adverse experiences. These are similar results to those that have already been seen in non-human mammals with simpler behaviour. The significance of the results did not depend on the ages of the children concerned; the period over which the outcomes were studied; the gene(s) chosen as targets; or the type of adverse experience. Some studies found that younger infants appeared to be more sensitive to differences in maternal care; prospective studies that monitor the same mother-infant pairs over a long period will be particularly useful here.

The authors also pointed out that, amongst the variables used to assess maternal caregiving, DNA methylation levels seem to be particularly sensitive to gentle maternal touch. This correlates with what is seen in other mammals, particularly rodents where maternal behaviour is assessed by observations of licking and grooming. This form of touch is sensed by nerves known as C-tactile fibres. Provenzi noted that the stimulation of these nerve fibres may be a mechanism through which maternal caregiving mediates DNA methylation and suggested this as another promising area for future studies. It will also be useful to examine the list of genes affected, many of which have several common, harmless variants. The extent to which this variation affects either the quality of parental caregiving or the extent to which an infant will respond to it is also worthy of future study, as is the interaction with hormones such as oxytocin (the so-called 'cuddle hormone' that is released during parent-infant and pair bonding).

Provenzi and his co-authors discussed questions and challenges that arise from human studies, in contrast with those on other mammals. It is easier to design a retrospective human study than a prospective one, and many retrospective studies rely on participants' memories, which may not be accurate. Both genome-wide studies and those focusing on target genes present specific challenges: the former, the need for robust theoretical underpinning to prevent the over-interpretation of unexpected correlations, and the latter, the reliance on inexact animal models. And, as it is impossible to extract DNA from the nervous systems of living people, there are questions about which tissues and cells should be used instead.

In conclusion, the co-authors outlined some areas where further research is needed into the epigenetic links between mothers' care of their young children and those children's future development. Long-term studies, particularly prospective ones, are needed to assess the protective effects of sensitive care of all young children, not only those who suffer from undue stress. They suggested the importance of physical touch, genetic variability in children and the differential responses of boys and girls as areas where further research would be particularly beneficial. More robust and detailed studies will provide further insight into the design of appropriate clinical interventions to help vulnerable mothers care for their babies and young children. Dr Clare Sansom

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