RESEARCH SUMMARY

THE VITAL ROLE OF OXYTOCIN IN INFANT EMOTIONAL DEVELOPMENT

Summaries of three related research papers

Introduction

Oxytocin is a chemical produced in the brain which is known colloquially as the 'cuddle hormone' because of its key role in bonding, particularly between parents and their infants. In new mothers, it is secreted in response to the stretching of the uterus during childbirth and the stimulation of the nipples during breastfeeding. It has been associated more generally with affection and bonding, and oxytocin levels have even been found to rise during affectionate play with a pet cat or dog. High levels of oxytocin in the saliva of infants and young children have been strongly associated with close parent-child bonding and positive social affect, which, in turn, are predictors for good social, emotional and even cognitive development as the child grows.

The research described in the three recently published papers summarised here illustrates the dependence between the oxytocin response in children and the way they are cared for by their parents, and particularly their mothers. This, like many aspects of human physiology and behaviour, is a system in which genetic and environmental influences intertwine, but sensitive parental care can stimulate oxytocin, parent-child bonding and pro-social behaviour in children even when their genetic background is problematic. Interestingly, the effect on bonding appears to be transmissible across at least three generations.

The first two of these papers were published in the same issue of the journal *Psychoneuroendocrinology* in April 2019, and the third was published in *Developmental Cognitive Neuroscience* in June 2019

Child's oxytocin response to mother-child interaction: The contribution of child genetics and maternal behaviour *Baião et al 2019*

Genetic and peripheral markers of the oxytocin system and parental care jointly support the cross-generational transmission of bonding across three generations *Fujiwara et al 2019*

Epigenetic modification of the oxytocin receptor gene is associated with emotion processing in the infant brain *Krol et al 2019*

Child's oxytocin response to mother-child interaction: The contribution of child genetics and maternal behaviour

Baião, R., Fearon, P., Belsky, J., Baptista, J., Carneiro, A., Pinto, R., Nogueira, M., Oliveir, C., Soares, I. and Mesquita, A.R. (**2019**).
Psychoneuroendocrinology **102**: 79–83

Like all hormones, oxytocin must bind to a receptor protein before it can trigger any of its physiological – and, in this case, psychological – effects. Like all proteins, this receptor takes slightly different forms in different people, resulting from tiny differences in the sequence of DNA bases that make up its gene. The smallest of these, involving changes to one single base in the DNA sequence, are known as single-nucleotide polymorphisms (or SNPs). In the case of the oxytocin receptor, a change from the base guanine to adenine (G to A) at one position in some people is known to cause it to bind oxytocin less strongly. There is some evidence that people who inherit the A-form of the gene (known as the A allele) from at least one parent have more pessimistic natures and lower self-esteem and are less likely to seek social support. These genetic differences, however, need to be set in the context of a strong environmental response. The oxytocin response in both rodent pups and human infants, which is known to be stimulated by nurturing care from their mothers, can also carry with it the positive outcomes of both closer bonding between mother and young, as well as – with human infants – encouraging more controlled and better regulated emotional responses.

A large, international group of scientists led by Ana Mesquita of the University of Minho, Portugal set out to investigate the contribution of genetic differences in the oxytocin receptor and the quality of maternal care, as these both relate to a young child's oxytocin response. A total of 88 healthy Portuguese pre-school children (between three and six years old) and their mothers were recruited into the study. Mother-child interactions were videotaped during a task involving three 5-minute periods in which 1) the child played with a challenging toy; 2) the mother completed an uninteresting task while the child was given little to do; and 3) free play. Saliva samples for oxytocin analysis were taken from the children before and after the whole interaction, and a separate sample was taken after the session for oxytocin receptor genotyping. The way in which each mother interacted with her child was assessed on two separate 9-point scales, one rating sensitivity (the mother's ability to interpret and respond to her child's signals) and the other cooperation (the mother's ability to respect her child's autonomy). The two scales were found to be highly correlated, and a combined 'sensitive responsiveness' score for each mother was recorded as a simple average of the two. The children were divided into two categories according to oxytocin receptor genotype: those with no 'A' alleles (the GG genotype; 50 children, or 56.8% of the sample) and those with at least one (GA or AA genotype; 38 children or 43.2%).

The researchers calculated the change in each child's oxytocin level during the interaction with his or her mother (the oxytocin response) and investigated how this varied with genotype and with the mother's sensitive responsiveness score. The childrens' oxytocin responses did not vary significantly either with their genotypes or the mother's scores: interesting differences only began to emerge when the variables

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were combined. Including all three factors in a regression analysis suggested a difference in oxytocin response with genotype only for the children of the less sensitive mothers; in this group, oxytocin levels decreased during the interaction in children with at least one 'A' allele and increased in those who lacked this 'A' allele altogether. Children of sensitive mothers had smaller oxytocin responses, regardless of their genotype.

Despite the limitations of this study – a low sample size, and the fact that, as is always the case in human studies, oxytocin levels in saliva were used as a proxy for those in the brain – the results seem to agree with the large body of research that suggests that oxytocin can be taken as a 'biomarker of social distress'. In particular, the oxytocin response to less sensitive maternal behaviour in children with at least one A allele suggests that these children did not find the interaction with their mothers particularly enjoyable. Taken together, these results suggest that further research into the interplay between genetic and relationship variables in determining a child's social and emotional responses should be valuable; it will be particularly interesting to look at the role of attachment here.

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Genetic and peripheral markers of the oxytocin system and parental care jointly support the cross-generational transmission of bonding across three generations

Fujiwara, T., Weisman, O., Ochi, M., Shirai, K., Matsumoto, K., Noguchi, E. and Feldman, R. (**2019**)

Psychoneuroendocrinology **102**: 172–181

The common observation that parenting is transmissible across the generations – that adults who were well cared for by their parents become more caring parents themselves – has been backed up by statistical studies. In parallel, parents who had themselves experienced good parental care have been found to have higher oxytocin levels than others, suggesting that oxytocin is likely to play a pivotal role in the transmission of parental care across the generations. Several studies have shown that there are variants of genes involved in the oxytocin system that pre-dispose infants to poor social interactions, and the adults they become later to certain subsequent psychiatric disorders: these variants have been termed 'risk alleles'. The genes concerned include the oxytocin receptor gene and a gene for a protein involved in the immune response that is simply known as *CD38*. These studies, taken together, suggest that the quality of the different bonds that individuals make throughout their life, from parents to childhood best friends, to romantic partners and then their own children, is transmissible between generations and depends on these genetic variants in the oxytocin system as well as on the quality of the relationships experienced. This provides a mechanism through which optimal or sub-optimal parental care can cascade down the generations.

A group of researchers led by Takeo Fujiwara at Tokyo Medical and Dental University in Japan investigated this hypothesis across three generations. They recruited 111 Japanese families into the study, each comprising a mother, her infant between 3 and 10 months of age and her own mother (maternal grandmother). All infants were healthy, and the mothers and most of the grandmothers were well educated and came from comfortable, middle-class backgrounds. Saliva was collected from each participant; oxytocin levels were measured, and, separately, DNA extracted and genotyped at two positions on the oxytocin receptor gene and one on *CD38*. One allele at each of those three positions had previously been identified as a risk allele. The grandmothers and mothers independently completed questionnaires about their childhood relationships with their own parents, their parenting styles and (past or present) relationships with their infant children. Statistical associations between oxytocin levels, genotypes and parenting quality were determined within and across the generations.

Between a third and half of the participants in each of the generations were found to have the risk allele at each of the three positions genotyped; there was no significant correlation between oxytocin levels (which were highly variable) and genotype at any position and in any generation. In both the mothers and the grandmothers, however, experience of high-quality care in their own childhoods correlated with caring but not over-protective behaviour with their own children. There was a high correlation between the grandmothers' memories of caregiving and the mothers' of receiving care, suggesting that these memories were accurate. Interestingly, mothers and

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grandmothers carrying some high-risk alleles remembered experiencing lower parental care on average than those with none of the high-risk ones. All risk genotypes were strongly transmitted from grandmother to mother and from mother to infant, so many of these women will have been cared for by a mother who also carried at least one of these alleles.

Some of the most significant correlations between parenting style, risk genotypes and oxytocin levels occurred with the poor parenting style characterised as 'over-protective'. This type of parenting is sometimes referred to as 'intrusive'. The mothers in the sample who had received over-protective care from their own mothers were found to respond less sensitively to their own infants than those who had not, but, oddly, only if they carried the 'low risk' genotype at one of the oxytocin receptor alleles. However, in the grandmothers' generation, it was women who carried a risk allele at a different position on the oxytocin receptor gene, and who had experienced over-protective parenting themselves, who showed poor parenting. The mothers who had experienced over-protective care had low levels of oxytocin. Oddly, and counter-intuitively, infants whose mothers showed 'rejecting' behaviour and who also carried non-risk alleles had just marginally higher ones than those with more caring mothers.

These results are complex, but they show without a doubt that mother-infant bonding is affected by both genetic differences in genes involved in the oxytocin response and the parenting experienced by both infant and mother. Some infants inherit a genetic resilience to poor parenting while others show an exceptionally sensitive response, and these differences are passed through the generations and can shape family behaviour.

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Epigenetic modification of the oxytocin receptor gene is associated with emotion processing in the infant brain
Krol, K.M., Puglia, M.H., Morris, J.P., Connelly, J.J. and Grossmann, T. (**2019**)
Developmental Cognitive Neuroscience **37**: 100648

The ability to distinguish emotions in human faces and voices is one of the earliest skills acquired by developing infants; a typical infant will be able to distinguish some emotions and respond appropriately at only seven months of age. Individuals of all ages differ in their response to emotion, and those infants who find this hardest to learn may develop mental health difficulties in later life.

The oxytocin system has been shown to be involved in emotion processing in experiments in which administration of oxytocin through the nasal passages leads to a stronger observed response to emotions. Differences in emotion processing between individuals arise from, among other things, differences in the genes that make up the oxytocin system. Not all of these, however, are the differences in DNA that are directly passed down between generations. Small modifications to the chemical structure of the DNA bases – so-called epigenetic changes – can arise throughout a person or animal's life, and these affect whether, when and how much of the respective protein will be synthesised from each gene; this in turn affects how oxytocin is processed in the brain.

DNA methylation, in which a tiny chemical group is added to one of the bases, is one such epigenetic change: less protein is synthesised from DNA that is more highly methylated. Increased methylation of one region of the oxytocin receptor gene leads to lower concentrations of the receptor protein being produced. In adults, for example, increased methylation in this region has been correlated with a higher risk of developing autism spectrum disorder and some mood disorders. Until now, however, little has been known about how methylation of the oxytocin receptor gene varies in infants and how this affects their ability to process emotions.

Kathleen Krol and her colleagues from the University of Virginia, Charlottesville, USA investigated this variation in 84 healthy, full-term Caucasian infants at the age when they will be learning to process emotions. Saliva was collected from each infant at five months of age. DNA was extracted from these samples and the methylation level of the appropriate segment of the oxytocin receptor gene measured. Previously, methylation levels measured in this way had been shown to be similar to those obtained from blood samples and to correlate with oxytocin expression levels, but only in prairie voles. To prove that this also applies to humans without subjecting the infants to blood tests, 206 adults of both genders had methylation levels determined from samples of both blood and saliva; they were, indeed, found to be similar. Emotion processing was tested at seven months by showing each infant randomised photographs of Caucasian actresses with a neutral expression that rapidly changed to show happiness, anger or fear. Brain activity was measured during these tests using functional near-infrared spectroscopy (fNIR), which generates an image of the brain highlighting its most active regions. The mother of each infant completed questionnaires about her infant's temperament and her own levels of anxiety and depression, including postpartum depression.

The fNIR results showed a strong response to the emotional faces in the inferior frontal cortex (IFC) in only the right hemisphere of the infant brain; no significant responses were recorded in the left hemisphere. The right IFC has been implicated in decision-making and impulse control, and the left IFC in speech and number processing. In the right IFC, the seven-month-old infants with high oxytocin receptor gene methylation responded differently to the different emotions than those with lower methylation levels did. Interestingly, infants with high methylation levels in this region of DNA responded more strongly to faces showing anger and fear than to those showing happiness; this situation was reversed in the infants with low methylation. Data from a previously published study showed a similar relationship between methylation of this gene and the response to positive and negative emotions in adults, indicating that these differences may persist as children develop. High methylation levels in this region of the oxytocin receptor gene in infancy might therefore predict emotional or even mental health problems in later life.

The researchers also tested the relationship between the infants' temperaments as assessed by their mothers, and their responses to the emotions. Infants with more fearful temperaments were found to respond more strongly to faces showing fear, and infants of mothers with higher self-reported scores for anxiety and depression also responded more strongly to the fearful faces. The oxytocin receptor genes in these infants also showed high levels of DNA methylation. Taken together, these results suggest that the oxytocin response system is important in the development of emotion processing in infants, and, specifically, that increased methylation of the oxytocin receptor gene and thus decreased levels of the receptor protein might be an early signal of a heightened response to fear and therefore probably also to perceived threats. They suggest a link between maternal behaviour and infant response, but more research is needed to determine the exact nature of that link.

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