RESEARCH SUMMARY

The Neuro-Environmental Loop of Plasticity: A Cross-Species Analysis of Parental Effects on Emotion Circuitry Development Following Typical and Adverse Caregiving

Callaghan, B.L. and Tottenham, N.

Neuropsychopharmacology REVIEWS (2016) 41, 163–176

Scientists from Freud in the nineteenth century onwards have suggested that the quality of the relationship between a child and his or her parents is an important factor – perhaps the most important one – in determining how well that child manages emotions in adulthood. The psychological model of attachment theory proposes that the bond between very young children and their main care-givers lays the foundation for the way children deal with social relationships as they mature. The validity of these theories has been underlined by the many studies that show a strong relationship between childhood adversity and severe emotional or mental problems in adult life. One recent study showed that 70% of a group of adults undergoing treatment for mental illness had experienced neglect or another type of trauma during childhood.

The biochemical and physiological mechanisms underlying the link between childhood relationships and emotional development have been studied for many years, both in humans and using non-human animal models. Bridget Callaghan and Nim Tottenham from the Department of Psychology at Columbia University, New York, USA have summarised much of this work in a wide-ranging review in the journal *Neuropsychopharmacology REVIEWS*. Callaghan and Tottenham began by describing important early work with rats by a psychiatrist, Myron Hofer. He observed the behaviour of rat pups that had been separated from their mothers for long periods, and concluded that infant rats learn in different ways in the presence and absence of their mothers. This is apparent in the specific area of 'fear learning', in which animals learn to avoid unpleasant stimuli. Infant rat pups will approach a neutral odour that is associated with a shock stimulus, but juvenile pups will avoid such an odour. Interestingly, pups at an intermediate stage tend to approach the odour only when their mother is present. This suggests that the mother rat's presence influences the way pups learn to respond to unpleasant stimuli.

Data from studies with human children also suggests that parents regulate the way their children learn to respond to emotional stimuli. The presence of a parent or other attached care-giver inhibits young children's responses to stressful and fearful stimuli but has no effect on those of adolescents. This suggests that there is a sensitive period during development when parents have a particularly strong influence on their children's emotional and physical regulation. This may at least partly explain the common findings that individuals whose parents were absent, cruel or severely disengaged during childhood are more prone to develop anxiety disorders than those reared in normal circumstances. Rats, also, learn fear response more quickly and experience more fearful responses if they are separated from their mothers or if their mothers are stressed.

We do not yet completely understand all the details of the neurobiological mechanisms through which parental engagement promotes emotional regulation in young mammals and human children. Most of the research in this area has focused on a circuit in the brain that is known to be involved in emotional regulation more generally: the amygdala-prefrontal cortex circuit. The amygdala is a small area within the temporal lobes of the brain that is predominantly involved in memory processing, decision-making, and emotional reactions; the prefrontal cortex (PFC) is an area at the front of the brain that is involved in complex cognitive functions, including the control of social behaviour.

Functional magnetic resonance imaging (fMRI) has consistently shown that the amygdala is activated in response to emotional and fearful stimuli, and it is known to be hyper-active in individuals suffering from emotional disorders. It continues to change in physiology and function until the end of adolescence; it is particularly active in childhood and appears, then, to be involved in the processing of childhood fears. In rat pups, high amygdala activity is associated with the time at which the pups change from approaching an odour associated with shock to avoiding it. The prefrontal cortex is believed to be involved in damping down these emotional responses in both humans and animals, and connectivity between the two brain regions increases throughout development. The decrease in the fear response generally associated with maturity is thought to be mediated by a growth in such connectivity, and human adults with weak amygdala-PFC connectivity tend to show exaggerated emotional responses. Studies in human adolescents have shown that connections between the amygdala and the PFC develop slowly until full maturity, and this finding has been replicated in animal studies.

Several studies have also shown that the physical presence of a parent is likely to mediate emotional stability in the offspring via the amygdala-prefrontal cortex circuit. In rat pups, the advance in learning the fear response associated with the absence of the mother seems to be mediated by increases in the activity of the amygdala and in levels of the stress hormone corticosterone there. In humans, amygdala reactivity is regulated by parental presence much more strongly in children than in adolescents. Amygdala activity and activity in the complete amygdala-PFC circuit can be lower – approaching the more 'mature' levels seen in adolescents – when children view pictures of their mothers; viewing pictures of strangers makes no difference. In other words, interacting with a parent can cause this crucial brain circuit to respond in a more adult-like way. Children and adolescents with higher (i.e. less mature) levels of amygdala activity are more anxious and less secure. Some of this modulation continues into adolescence: youths with anxiety disorders show more activity in the amygdala than healthy youths, but this activity can decrease to normal levels in the presence of the anxious youths' parents.

All these studies suggest that there is a particularly sensitive period in the development of each mammalian species when the presence of a parent, and particularly of the mother, is able to influence the activity of the amygdala-PFC circuit and thus emotional reactivity and learning. This lasts for a few days in rodents but for the whole of childhood in humans and the equivalent developmental stage in

Website: http://www.whataboutthechildren.org.uk
What About The Children? (***WATCh?***)**:** Company No. 5252973 - Reg. Charity No. 1108816

monkeys. The end of this sensitive period corresponds to both the attainment of mature levels of amygdala activity and growing independence from the parents. This also implies that if the parents are absent or if the parent-offspring relationship is impaired the circuit will not mature in the normal way.

It appears that parental absence or adverse rearing can bring the period of plasticity in emotional regulation to an end earlier. This is certainly the case in rats, where the odour-avoidance response is learned earlier when pups experience fragmented maternal care. Early separation from the mother also speeds up the production of the myelin sheath that surrounds nerve cells (neurons) in the amygdala; this myelinisation is thought to increase circuit stabilisation. This supports the idea that early independence from the mother, for whatever reason, terminates the sensitive period and thus shortens the period during which the amygdala-PFC circuits can mature.

It is clearly impossible to replicate rodent studies in humans, but some insight can be gained from studying individuals reared apart from their parents, such as those who grew up in institutions. Interestingly, the end of the 'childhood' period of amygdala-PFC plasticity typically occurs earlier in such individuals than in those reared in their birth families. This early maturation may have a short-term benefit in allowing adolescents in this situation to cope better with an enforced early independence. Other studies have shown that adolescents who had experienced childhood adversity had larger amygdalae than those who had been reared more normally, and this increase in amygdala size was correlated with an increased incidence of depression. Callahagn and Tottenham ended this section of their review by summing up the evidence that chronic parental deprivation or parental stress in all mammalian species results in a shortening of the sensitive period for the amygdala-PFC circuit, leading to an increase in amygdala reactivity and, potentially, to a decrease in emotional regulation that may persist throughout life.

They then presented evidence to suggest that the changes in plasticity in the amygdala-PFC circuit is related to changes in dependence on the main caregiver during development. Infants are completely dependent on their caregivers, and this seems to protect this circuit from external influences. Plasticity increases when the growing child (or pup) becomes physically independent through learning to walk while remaining completely dependent in other ways, and only decreases again when independence begins to increase in adolescence. An early closure of this window, which can occur with childhood deprivation, may have a long-lasting adverse effect on emotional stability. Interestingly, however, some other people – close friends of the same gender in early adolescence, and romantic partners in adulthood – can play a similar role in buffering stressful experiences in the same way that a parent does in childhood.

In concluding the review, Callaghan and Tottenham proposed a model they termed the 'neuro-environmental loop' to describe the interaction between the parent-child relationship, the neurobiology of the amygdala-PFC circuit, and behaviour. This suggests that there is an optimum point in early childhood when the child is first able to explore his or her environment but is very dependent on parental care when the amygdala-PFC circuit becomes sensitive to external influence. Supportive interactions

Website: http://www.whataboutthechildren.org.uk
What About The Children? (***WATCh?***)**:** Company No. 5252973 - Reg. Charity No. 1108816

between parent and child during this period lead to the modulation of this circuit and, gradually, to the development of connections between these two structures that dampen the reactivity of the amygdala and that are associated with maturity. In other words, children who experience frequent supportive care from their parents will more easily develop mature reactions to emotional stress. This may arise through suppression of the release of the stress hormone corticosterone by the presence of the parent. Stabilisation of the mature circuits corresponds to increased independence as the child moves into adolescence. Furthermore, childhood deprivation leading to precocious independence shuts off the sensitive period, leading to an increase in emotional vulnerability that may last throughout life. Further research, and, in particular, longitudinal studies of subjects across the whole developmental period, will be necessary to further clarify the mechanisms of amygdala-PFC development and identify ways of helping individuals with impaired amygdala-PFC circuits as a result of parental deprivation or neglect in childhood.

Dr C. Sansom

Website: http://www.whataboutthechildren.org.uk
What About The Children? (***WATCh?***)**:** Company No. 5252973 - Reg. Charity No. 1108816