



RESEARCH SUMMARY

Developmental pathways to amygdala-prefrontal function and internalizing symptoms in adolescence.

Burghy, C.A., Stodola, D.E., Ruttley, P.L., Molloy, E.K., Armstrong, J.M., Oler, J.A., Fox, M.E., Hayes, A.S., Kalin, N.H., Essex, M.J., Davidson, R.J. & Birn, R.M.

Nature Neuroscience (2012) doi:10.1038/nn.3257; published online 11 November 2012.

Early life stress (ELS) is now understood to be a risk factor for health problems in later life. This paper pins down the general mechanism of this process through the hypothalamic-pituitary-adrenal (HPA) axis for girls but not for boys. The mediator is the stress hormone cortisol which exerts its effects through the amygdala-ventromedial pre-frontal cortex (vmPFC). The amygdala and vmPFC are regions in the brain that are involved in affective reactivity and regulation, affective reactivity being a characteristic that describes how humans experience emotions and interact both with people and with their surroundings. Cortisol binds to glucocorticoid receptors in the prefrontal cortex, where there are a large number of these receptors. The amygdala is also associated with ELS and anxiety in female non-human mammals.

This paper uses data from the ongoing longitudinal investigation from the 'Wisconsin Study of Families and Work' programme; the development of children was followed from birth to adulthood. All participants had their ELS exposure in infancy measured for the following: early maternal stress, depressive symptoms, parenting stress, marital conflict, role overload and financial stress; measurements were taken at 1, 4 and 12 months of age. Each member of the cohort had salivary samples determined for basal cortisol levels at age 4.5 years; these are termed childhood cortisol levels. From this cohort, a sample of 57 people, now aged 18 years i.e. adolescent, was selected with self-reported psychiatric symptoms. Each person was given a functional connectivity magnetic resonance image (fcMRI) scan of the brain to determine resting-state functional connectivity (rs-FC) between the amygdala and frontal cortex. This simply means that the researchers were looking at the spontaneous natural state of the brain circuits, independent of any given task. Resting cortisol levels were measured in the adolescents. Adolescent life stress measurements were also determined. Anxiety and depression were the pathological states that were tracked in the analysis. Of the 57 people in the sample, 28 were female. The results were analysed using Pearson-*r* bivariate correlation statistics, which is a statistical test to measure the strength of a correlation, and the value of the strength is termed "*r*".

In statistics, *p* values estimate the probability of the results being generated purely by chance. A *p* value of 0.05, therefore, would show that there is only a 5% probability of the results being chance, i.e. not at all likely to be 'by chance'. There was a significant (*p*<0.05) correlation for Early Life Stress and the amount of childhood cortisol for females *r*=0.45 (strong correlation), but not for males *r*=0.08 (insignificant correlation).

(this Summary may be photocopied)

From the fcMRI scans, the correlation between childhood cortisol levels and adolescent amygdala-vmPFC rs-FC was highly significant ($p < 0.001$) (one tenth of one percent) with $r = 0.78$ for females, but for males the $r = 0.19$ was not significant. For simplicity, this means that the hard-wiring of the two brain circuits in the resting state showed that high cortisol levels gives you low connectivity and low cortisol gives you high connectivity – i.e. the higher the cortisol levels the greater the suppression of the normal wiring. Also there is a clear difference between the genders. The relationship between female cortisol levels in childhood and connectivity to the left amygdala in female adolescents is inverse linear; that is to say, high levels of childhood cortisol are associated with low levels of connectivity in adolescence.

Statistical analysis for adolescent anxiety showed a significant ($p < 0.05$) correlation with childhood cortisol in females with $r = 0.47$ but no significant correlation in males ($r = 0.13$). Similarly, there was a statistically significant inverse correlation between anxiety and the two brain circuits in the adolescent female, but not in males. With adolescent depression, significant correlation was found with the two brain circuits in adolescent females but not in males.

These results confirm that early life stress in females causes elevated cortisol levels in childhood; this in turn affects the brain connectivity between the amygdala and the vmPFC (emotion-related brain circuits) in the resting state that is propagated into adolescence. These changes correlate, in the female brain, with symptoms of anxiety and depression in adolescence. Differences in gender are profound.

(Note from summariser: Further research would be needed to show up which pathways are more affected, in the long term, in males from a rise in persistent cortisol levels in infancy. Present research results, looking at adult reactions to stress, would indicate that whereas stress in females activates emotional centres, with males it activates testosterone release.)

Dr. P. M. Dean