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Kaleidoscope

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It is an oft-quoted mantra that people in contemporary Western society are encouraged to blame their parents for any later woes. It is clear that the maternal bond is of primal importance in early life, but how do any *prenatal* influences affect a child, such as having a mother with a major depressive disorder during pregnancy? Fetal exposure to maternal depression has now been shown[1] to be associated with cortical thinning in children at 9 years of age, with the pattern of thinning similar to that seen in adults with, or at increased risk of, depression. These effects were most pronounced for the exposure at 25 weeks' gestation, and were maximal in the prefrontal cortices. In this study the significant association between maternal depression and later childhood externalising behaviour problems was mediated by the cortical thinning; the authors argue that this may serve as a prodromal risk indicator for later affective disorders.

It is hardly surprising that maternal depression can also have an impact on the well-being of children *ex utero*. Weissman *et al*[2] followed the progress of mothers with depression randomised to receive escitalopram, bupropion, or their combination over 12 weeks; their children's well-being was independently assessed. There were no between-group differences in outcomes for the women, but the effect of their improvement in mood upon their children depended on the mother's baseline symptom profile. Children of mothers with low 'negative affectivity' improved in all groups, but those with mothers with high negative affectivity only improved when their mothers were on escitalopram. Exploratory analyses indicated that women in the escitalopram group reported significant improvements in their ability to listen and talk to their children; the children described the mothers in this group as becoming more caring during the same period. The construct of negative affectivity, which incorporates the domains of guilt, irritability, and fear/anxiety, has a possible biological underpinning mediated by aberrant serotonergic functioning; the authors posit that depressed mothers with greater degrees of these symptoms may require serotonin-specific treatment. Both of these studies remind us of the importance of timely and evidence-based care during this vulnerable period.

The menopause is associated with increased rates of mental ill health, with a two- to threefold increase in depression alone. Although linked with complex neuroendocrine and psychological factors, any associated brain changes are poorly understood. Recent work on female macaque monkeys has demonstrated[3] that ovarian steroids help regulate gene expression related to DNA repair in serotonergic neurons. Gordon *et al*[4] offer a novel mechanism that moves beyond a simple model involving low basal levels of hormones; they propose that type A γ-aminobutyric acid ($GABA_A$) receptors, in the face of *fluctuating* ovarian hormones and derived neurosteroids, become unable to maintain the normal plasticity of GABAergic tone, leading to hypothalamic–pituitary–adrenal (HPA) dysfunction. It is this latter change that leaves menopausal women more sensitive to subsequent stressors, and ultimately vulnerable to depression. Previous large studies, such as the Women's Health Initiative, have in general produced negative findings for the therapeutic use of hormonal treatments in depression; however, an interpretation of the current data is that future work should look at much earlier interventions in perimenopausal populations.

In 1989, Black Francis helped us understand divinity and the afterlife by producing the following enumeration: 'If man is 5, and the devil is 6, then God is 7'. If you ask people to represent this as a number line, they would invariably put man (5) on the left, and God (7) on the right (based on the size of the numbers). Humans draw number lines from left to right, with lower numbers strictly to the left of higher numbers, and indeed have a general 'pseudo-neglect' bias to primarily attend to objects on the left side of space. The 'mental number line' is purported to be an intrinsic neural property of perception, but has also been suggested to be secondary to cultural factors such as the direction that text is written in one's first language; however, numerical competency preceded the emergence of language, and indeed it is evident to varying degrees in non-human species. Rugani *et al*[5] have now shown that chicks (that is, baby chickens) also possess this left-to-right ordering, adding weight to the bias being more than just due to culture. Three-day-old chicks were first trained by being placed in front of a central panel with a fixed and constant number of dots. Then, in testing, each chick was presented with two panels (one left and the other right of centre), both containing the same number of dots but which were now either much larger or smaller in number than the training stimulus. When the number of dots in the test phase was larger than the training one, the chicks favoured the right panel. Conversely, when there were fewer dots on the testing panel, chicks ambled over to the left panel. The result persisted even when area, colour and shape of the dot patterns were controlled for; analogous to humans, chicks associated smaller numbers with the left, and larger numbers with the right. The authors argue that this spatial mapping of numbers may be a universal cognitive strategy available from shortly after birth, and although modifiable by culture, it is written into the architecture of our brains. It raises the interesting question of how many other such biases are predetermined by our brain structure.

We tend to think of pain relief and substance misuse when considering the brain's opioid system, but of course its functions extend beyond this. Two recent papers have looked at better understanding the roles of the opioid δ (delta, or DOR) and μ (mu, or MOR) receptors in emotional processing. As well as physical pain control, the DOR is involved in impulsivity, learning, and memory processing, although its neuronal circuitry remains unclear. Work on DOR knockout mice[6] demonstrated that the receptor has a role in locomotor activity, but a second and unanticipated finding was that the DOR altered anxiety processing. The mutant mice, lacking this opioid receptor, had considerably less anxiety-related behaviour during stress testing, with the data indicating that GABAergic forebrain neurons were contributing to increased anxiety in the healthy controls. The results are interesting and somewhat counterintuitive as other rodent DOR knockout studies have generally shown *increased* anxiety, and that DOR agonists can be anxiolytic. Synthesising these disparate findings, the DOR appears to have a more nuanced role in anxiety than previously believed, forebrain receptors being anxiogenic, midbrain (particularly in the amygdala) anxiolytic.

The MOR also has an established role in reducing physical pain, and Hsu *et al*[7] have used positron emission tomography (PET) to evaluate its activation during *emotional* pain. Both healthy controls and medication-free individuals with major depressive disorders were examined during a social rejection paradigm. When faced with social rejection, those with depression showed reduced endogenous opioid release in brain regions regulating stress, mood, and motivation, and a slower emotional recovery than healthy controls. Both groups reported an increased positive affect during a social acceptance task, but only the

controls showed enhanced social motivation, which was correlated with greater opioid release in the reward structure of the nucleus accumbens. Although the role of opioid dysfunction in depression has yet to be clarified, these data suggest that alterations may contribute to hindered recovery from negative interactions and decreased pleasure from positive ones. All of which adds succour to Sydenham's notion that 'Among the remedies which it has pleased Almighty God to give to man to relieve his sufferings, none is so universal and so efficacious as opium'.

There has been interest in the use of deep brain stimulation (DBS) as a potential treatment for substance misuse. Synaptic plasticity underlies the brain's ability to implement adaptive change, and in substance dependence this results in maladaptive behaviours; DBS can alter subcortical neural circuit remodelling, although its precise mechanisms of modification have not been elucidated. In *Science*, Creed *et al*[8] describe a novel DBS experiment on rodents subjected to a cocaine sensitisation protocol. Rather than developing tolerance and a lessening of effect, a sensitisation model of drug addiction produces progressively greater responses (here increased locomotion to obtain cocaine) and also explains the generalisation of the response to unconditioned stimuli associated with the drug exposure. In rodents on cocaine this occurs after only five drug injections and persists for several months. Neurophysiologically (in rodents and humans) the reward centre of the nucleus accumbens (NAc) receives glutamatergic projections onto D_1 (dopamine D_1 receptor expressing) medium spiny neurons that are strengthened in response to repeat cocaine administration. Combining low-frequency DBS of the NAc shell with a dopamine D_1 receptor antagonist obliterated this adaptation and the drug-adaptive behaviour. High- or low-frequency DBS alone did not have this effect. The effect of low- but not high-frequency DBS indicates that the induction of metabotropic glutamatergic long-term depression is the therapeutic end-step (differing stimulation frequencies upregulate different receptor subtypes); the need for medication augmentation suggests that DBS alone may be too non-specific and unhelpfully produce dopamine release that limits therapeutic changes.

Finally, the topical question of how ideologies can radicalise. What is it about a speaker that can make them and their ideas charismatic and persuasive, and how is this processed in the brain? A study[9] of German political figures' speeches has shown that powerful deliveries evoked strong alignment of brain activation among their listeners. Assessment of inter-individual correlations demonstrated that rhetorically commanding speeches elicited strong temporal alignment of activity of the superior temporal gyri and the medial prefrontal cortex among listeners, but weaker talks – which are still complex stimuli and must activate similar brain regions – evoked more heterogeneous activity. Influential presentations appear to very much captivate the regions of the brain linked with auditory processing of speech comprehension and social cognition.

Can neuroscience help inform us of what brain alterations might be related to more radicalised opinions? Over 100 individuals with various traumatic brain injuries were tested[10] on a political belief task, rating opinions on the topics of welfare, the economy, political involvement, civil rights, war and security. Those with specific ventromedial prefrontal cortex (vmPFC) lesions showed greater radicalism – but not individualism or conservatism – and this region appears critical for appropriately valuing radical political behaviours as well as social and moral judgements. The looming general election might provoke interest in this from political parties keen to shape your views, especially if you also exhibit the aforementioned 'pseudo-neglect' and display a bias towards the left.

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