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Kaleidoscope

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Given the increased opportunity to communicate – Snapchat, Instagram, Twitter, Facebook – young people seem connected in ways hard to imagine even 10 years ago, but does it make them feel less isolated? Matthews *et al*[1] explored data from the Environmental Risk Longitudinal Twin Study, a birth cohort of over 2000 individuals born in England and Wales between 1994 and 1995, looking in particular at the experience of loneliness at the age of 18. Loneliness occurred in 23–31% (5–7% reporting feeling this often), was equally spread across genders and socio-economic backgrounds, and was associated with greater rates of unemployment and less confidence about future prospects. Lonely young people were also more likely to have current mental health problems, engage in more risky physical health behaviour such as smoking and getting less exercise, and have more negative strategies to cope with stress. It was linked with past experiences of bullying, social isolation and mental health problems. It is easy to see loneliness as an issue of old age; however, data suggest it is actually more common in the young. Paradoxically, the loneliest young adults had the greatest rates of social media use, a compulsion that appeared to remove them from other activities and real human contact. We look nostalgically, perhaps, at young people, imagining they all have fun-filled busy social lives; it simply is not true for very many of them.

> **'may my heart always be open to little**
> **birds who are the secrets of living**
> **whatever they sing is better than to know'**[2]

taught e e cummings. Darwinism suggests that one of the drivers for human cognitive development might be female mate choice; choosing smart males and thus selecting genes for intelligence. It makes sense as a concept; picking someone with brains intuitively feels a sensible survival strategy. However, it is been hard to test and prove – one factor among many in our often complex love lives as a species – but good fodder if you wish to start an animated debate with others. Chen *et al*[3] add a twist to this in a study on budgerigars. Female budgies' preferences were first tested in an observing phase, where they were able to choose between two males. The less preferred male was then trained to solve two foraging problems to access food, and after that the females again observed the same males, but this time watched as they tried to get food by opening a 'puzzle box'. The previously less-favoured (but now trained) males understandably outperformed the others, and the females' preferences significantly shifted to these erstwhile disregarded, but now seemingly more-than-bird-brained, Lotharios. Such a shift did not happen in the control trials of all males having free access to food, and they were equally disinterested in observing 'clever' females who had been taught this trick. It is the first time observed intelligence has been shown to drive mate choice: how well does it map onto humans? We will let you and your friends argue that out: to spice things up, we recommend dividing the discussion into 'current' and 'ex-partners'.

Understanding the system-level dynamics of how memories are physically stored in the brain remains one of the great scientific challenges. It has been proposed that memory formation broadly divides into a fast, hippocampus-dependent mechanism and a slower transfer to a more permanent neocortical representation. The 'fast' mechanism involves synaptic plasticity and reorganisation in the hippocampus dependent on intracellular signalling and protein synthesis. Longer-term memory results from 'system consolidation' and although thought to be initially hippocampal-dependent, consolidation results in persistent cortical representations that, over time, are dissociated from the hippocampus. The intricacies of this consolidation process have been studied in rodents, but not demonstrated in humans. So far, using functional magnetic resonance imaging (fMRI), it has not been possible to dissociate activity that represents an actual memory representation in the cortex (an 'engram') from activity induced by input from another region down- or upstream in the network. One defining principle of an engram is that there is identifiable structural change in the neuronal substrate. To this end, Brodt *et al*[4] describe a study that combines fMRI with diffusion weighted MRI (DW-MRI) in an attempt to locate engrams when learning object–location associations. They scanned 39 and 33 participants for the learning versus control (no learning) groups, respectively. In the fMRI component, whole-brain analyses (comparing learning versus control groups) of successful 'retrieval' trials showed that the precuneus and dorsal visual stream was reliably activated with its blood oxygen level-dependent (BOLD) response increasing as a function of experience in the task. This observed regional BOLD response persisted, evidenced when repeating the retrieval trials 12 h after the first learning session. The hippocampus was, however, only reliably activated in early 'encoding' trials. The authors suggest that the precuneus, part of the parietal cortex, 'holds' a representation for retrieved information.

DW-MRI yields the mean diffusivity measure and, as Brodt *et al* describe, is proposed to decrease in correspondence with structural changes associated with learning (for example changes in synaptic density). The DW-MRI scans were acquired prior to the object-association learning task, and then again after the 12 h break in both the learning and control groups. It was shown that after 12 h, there are quantifiable differences in the learning and control groups' mean diffusivity measure bilaterally in the precuneus and in the ventral and dorsal visual processing streams. The changes in mean diffusivity were also moderately correlated with retention-recall performance after the 12 h interval. Together, their results suggest that structural changes accompany functional activity in a way that support adaptation in the neural substrate consistent with the establishment on engrams.

Where antidepressants work, the effects are upstream of the synapse (despite the occasional antipsychiatry rant, none of us propound a 'chemical imbalance' theory). Understanding this in more detail should facilitate the development of the next generation of medications. Gulbins and colleagues[5] show that the antidepressants fluoxetine and amitriptyline induce autophagy in hippocampal neurons via gradual accumulation of sphingomyelin in lysosomes and Golgi membranes, and ceramide in the endoplasmic reticulum. Intriguingly although antidepressants required about 12 days to produce these changes – fitting with clinical effects – direct inhibition of sphingomyelin synthases with a novel agent (tricyclodecan-9-yl-xanthogenate) did so in just 3 days, with rapid autophagy and reversal of signs of major depressive disorder in an animal model. The data fit with other studies showing that environmental stressors and cortisol inhibits autophagy, and indeed the authors note that circadian patterns of autophagy map those seen symptomatically in depression.

Another intracellular protein, brain-derived neurotrophic factor (BDNF) has a long association with depression, with recent work showing that its activity-dependent release in the medial prefrontal cortex is critical for the rapid antidepressant effects of ketamine. BDNF is known to stimulate expression and neuroblastoma release of vascular endothelial growth factor (VEGF). These

growth factors act via independent tyrosine kinase receptors, but also have overlapping signalling pathways, and Deyama *et al* tested the impact of blocking VEGF through a neutralising antibody and neuron-specific depletion.[6] A single intra-medial prefrontal cortex infusion of BDNF produced rapid antidepressant effects like those seen via ketamine. However, VEGF inhibition stopped BDNF-induction of dendrite complexity and its antidepressant effects. The relationship between BDNF and VEGF appeared reciprocal and interdependent: each requires the presence of the other to work. Two studies helping unpeel the biology of depression; both offering new potential pharmacological targets.

There has been progress towards understanding how neuromodulation by dopamine actually affects the function of the brain at the systems level; not least demonstrations of reward processing in the mesolimbic system, and tentatively, negative symptoms of schizophrenia in the mesocortical pathway. Beyond reward processing, one idea is that dopamine receptors can facilitate 'filtering' of inputs to neuronal circuits such that the activity of these populations of neurons can form temporally stable representations, for example in the prefrontal cortex. Although there is a mass of evidence from rat, primate and *in vitro* neurophysiology, it is harder to experimentally manipulate and observe changes in humans – many folk being awkwardly resistant to having holes drilled into their head. One method proposed in humans is acute tyrosine and phenylalanine depletion (ATPD) where experimental participants are given an amino acid drink, which in principle lowers the amount of tyrosine and phenylalanine available as precursors for dopamine synthesis in the brain.

Shafiei *et al*[7] used resting state fMRI in 51 participants who, in a crossover, randomised and masked study, underwent separate days of scanning with either a balanced (BAL) or ATPD protocol prior to scanning. This analysis showed a widespread increase in variability over the brain, but most notably in regions of the somatomotor and salience networks. Separately, a functional connectivity network analysis then identified nine networks (including the somatomotor and salience networks). Contrasting the BAL and ATPD groups, the connectivity indices for these networks was negatively correlated ($r = -0.59$) with regional signal variability, suggesting that when signal variability increases, functional connectivity decreases. The authors conclude that when dopamine is depleted by ATPD, there is a quantifiable reduction in connectivity accompanied by a concomitant increase in regional BOLD signal variability. Dopamine appears to stabilise neural signalling and dopamine-dependent signal variability helps functionally embed individual brain regions into larger-scale networks.

Several recent Kaleidoscopes have noted positive results for hormonal treatment of postnatal depression; well what about men? This might invoke Monty Python's *Life of Brian* for you – 'Suppose you agree that he can't actually have babies, not having a womb, which is nobody's fault, not even the Romans', but that he can have the right to have babies'. Well, to return to science, Walther *et al* meta-analysed data on testosterone treatment in men with major depressive disorders.[8] Testosterone is neuroactive including in influencing affect, and it alters serotonin release, but any role in mental illness has been heavily debated. Low testosterone has been shown to be related with depression in some studies, but data are mixed and it is not a treatment recommended by standard guidelines. Here 27 randomised controlled trials met inclusion criteria, encompassing almost 2000 men. Compared with placebo, the hormonal treatment was associated with a moderate although significant reduction in depressive symptoms, and it was just as acceptable from a side-effect viewpoint. Dosage was an important modifier, with effects most robust when >500 mg/week. Interestingly, neither age nor participants' baseline testosterone levels predicted outcomes, and the results thus do not support a hypothesis that treatment is rectifying an endocrine abnormality. The field of, and evidence base for, psychoendocrinology is growing; are clinical services ready to meet this?

Finally, many people have expressed concern that the current global political climate is fostering xenophobia and frank racism. Cultural beliefs change and we are all subject to wider and deeper currents altering attitudes over even relatively short periods; to take a somewhat inane example, the rather soporific 1990s TV show *Friends* is now argued by some to be upsetting contemporary mores and be unsuitable for broadcasting.[9] To a more important example, Charlesworth & Banaji note how, in 1958, only 4% of White Americans approved of Black–White marriages, but the figure was 87% by 2013 (it is perhaps more surprising that by 2013 13% of the population still objected).[10] They report on the first comparative analysis of patterns of long-term change across social group attitudes, assessing frankly expressed opinions and, through an implicit association test (IAT), implicit attitudes. Over the decade examined, all explicit responses showed changes towards attitude neutrality – in other words, less overtly expressed hostility – in the six explored categories of sexual orientation, race, skin tone, age, disability and body weight. However, interestingly, the implicit responses only showed such positive change regarding sexual orientation, race and skin tone and were stable for attitudes to age and disability – that is, no improvement from 2006 – while attitudes to body weight had worsened. Implicit attitudes to sexuality changed across all cohorts, showing a broad societal shift, whereas those to race and skin tone showed faster change in younger people. Intriguing findings from the USA, which feel – to the Kaleidoscope team at least – to have face validity for us here in the UK. The IAT is fascinating, and if you'd like to explore your own neutrality, test yourself at: https://implicit.harvard.edu/implicit/takeatest.html. You might have noticed that the study goes up to 2016, just before Brexit and Trump: an update on change over the past 3 years feels warranted.

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