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Kaleidoscope

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'Psychobiotics' is your new word this month: live micro-organisms with mental health benefits. We've previously noted the links between the gut microbiome and changes in cognition and psychopathology.[1] Now, Allen and colleagues[2] test an intervention – using the bacterium *Bifidobacterium longum* 1714 – in 22 healthy volunteers who undertook cognitive assessments, resting electro-encephalography (EEG), and a social stress test at baseline, post-placebo, and post-psychobiotic. The active intervention was associated with reduced cortisol levels and subjective anxiety in response to the stress test, as well as lower levels of self-reported stress. It also resulted in enhanced frontal midline EEG mobility, which is representative of prefrontal cortical activity, and modest improvements in visuospatial memory performance. The authors propose a precision strategy, to rationally test particular candidate bacteria strains – rather than the 'probiotic cocktail' often administered – against specific psychopathology.

As an interesting corollary, writing in *Neuropsychopharmacology*, Raison & Miller[3] take an evolutionary approach to depression, suggesting that the environmental and genetic risk factors, the acute phase inflammatory response, and female preponderance are all consequences of humans' interactions with microbes over millennia. Provocatively, they propose that major depressive disorders have adaptive functions that ensure survival, not through – as has been suggested in social evolutionary theories – mechanisms of avoiding conflict with more powerful individuals, but via managing relationships with the pathogens with which we co-evolved. The 'cost' of depression might be offset by an anti-pathogen heightened immune response, or as a form of 'sickness behaviour' wherein a responding immune system invoking depression might protect a vulnerable individual through social avoidance/energy conservation. Pending more research on these fascinating topics, we anticipate increased hyperbole from probiotic yogurt commercials.

There has been much political debate on minimum pricing of alcohol, but how effective are such policies? In December 2016, a collaboration of 43 organisations wrote to the Chancellor of the Exchequer urging him to implement this previously promised intervention.[4] Now, writing in the *Lancet*, Burton and colleagues[5] give a masterful overview of the evidence. They note alcohol harms to be driven by three main factors: affordability, availability and social acceptability. To some, this may sound suspiciously similar to the trilogy of values espoused for success in private practice. Despite variability across studies, the literature broadly supports policies that tackle affordability, marketing, and late-night sales. The overall provision of information and education increased awareness but did not have the desired impact on longer-lasting changes, although individually directed interventions aimed at at-risk drinkers and the use of enforced legislation are effective. In conclusion, they note that there is a 'rich evidence base' to support the decisions of policy makers in reducing alcohol-related harm. The UK population drinks twice what it did 40 years ago (significantly driven by an increase in female alcohol consumption, higher-strength beverages, and reduced relative prices), at an estimated annual societal cost of £21 billion: we hope the government is reading and listening.

Medical school can be gruelling, so how common is mental ill-health in medical students? Rotenstein *et al*[6] identified 195 studies of medical students ($N = 129\,123$) from 47 countries. Meta-analysis found an overall pooled prevalence of depressive symptoms in just over 27%, of whom less than one in six had sought psychiatric help. Of particular concern, suicidal ideation occurred in 11%. There was considerable variation between individual studies, but no major differences between different geographical regions, or between preclinical and clinical students. To contextualise the findings, the authors contrast against a typical 12-month prevalence of depression of 9.3% in 18- to 25-year-olds in the general population. We can all recollect the stress and pressures of being a medical student, but we don't yet have robust data on the specific factors driving these grim figures, or the consequences for students' subsequent mental health in the longer term.

What can we do to help? Panagioti *et al*[7] reviewed different interventions to reduce burnout in physicians, including evaluating the impact of physician characteristics and different healthcare settings. Burnout was identified as a problem of whole organisations and their culture, not individuals – notably: excess workload, employees not having control over their work, and prolonged stress. Their findings supported intervention programmes, albeit that the benefits were typically small. Organisational-level interventions that target improvements in the working environment were most effective, and those applied to senior clinicians and doctors in primary care were more effective than with junior staff and hospital-based doctors. There was a large variation in the types of organisational approaches, though structural changes, enhanced team communication, and encouragement for team-working were typically most effective. Individual interventions appear to be a less fruitful avenue, fitting with the concept that any 'problem' is not in the person.

The cyberpunk author William Gibson wrote that 'Time moves in one direction, memory in another'. As some of us try to erase the upheavals wrought in 2016, science continues to try to find out how to reactivate forgotten memories. Rose *et al*[8] presented participants with two items to memorise, followed by a cue that indicated which item they would later be tested on – essentially, the cued item was hypothesised to be 'attended to' and be actively represented in working memory, whilst the other item would become latent (the 'unattended memory item' or UMI). Later in the trial, the participant was given a second cue which indicated whether or not to use the attended or the unattended item to respond to a memory probe. Using pattern recognition techniques applied to functional magnetic resonance imaging blood oxygen-level dependent (fMRI BOLD) data, they showed how the neural representation of the UMI decays to baseline but can be reactivated if required by the second cue. Using a single transcranial magnetic stimulation (TMS) pulse – delivered after the cue that assigned items to either attended or unattended states, but before the retrieval probe – a similar effect was observed with EEG activity correlating with the UMI reappearance. The findings support a synaptic theory of working memory: information can be held in working memory via 'activity silent' synaptic mechanisms.

If forgetting is more your bag, then Hebert-Chatelain *et al*[9] show that after training mice on a novel object recognition task, administering cannabinoid receptor agonists induced amnesia via an intracellular cascade in mitochondria. Agonism of mitochondrial CB1 cannabinoid receptors was shown to reduce excitatory synaptic transmission but knock-out mice lacking CB1 receptors in the mitochondria of their hippocampal cells did not demonstrate reduction in metabolism when given

cannabinoids, and consequently, did not show cannabinoid-induced amnesia. The well-recognised acute amnesic effects of cannabis on the brain thus may involve alteration to mitochondria; further, this suggests how mitochondria can act as primary acute regulators of normal cognitive functioning.

The link between stress and impaired memory performance seems intuitive but previous studies have not controlled for the quality of encoding – that is, participants have been given the instruction to 'memorise' the stimuli, but how they achieve this was left to the participant. Different strategies can lead to different qualities of memorisation – the strength of encoding is demonstrated by recall success – so current research showing a link between stress and recall are confounded by the cognitive strategy. Writing in *Science*, Smith *et al*[10] designed an experiment where they use retrieval practice: the familiar tactic of taking lots of practice tests before the 'final exam'. They divided 120 participants into two groups; one used study practice (SP), the other retrieval practice (RP): the RP group simply attempted repeated free recall of the stimuli without feedback; the SP group re-studied the stimuli. The stimuli were concrete nouns or images of concrete nouns, balanced so half had neutral and half had a negative valence. Twenty-four hours later, 30 SP and 30 RP group participants underwent stress induction (confirmed by physiological measures) consisting of speeches and solving mathematics problems in front of 2 judges and 3 of their peers, while the remainder completed a time-matched non-stressful task.

Both the SP and RP groups in the stress/non-stress conditions were tested for recall success immediately after the stressful (non-stressful) event, and again 25 min later. On the delayed test, the stressed SP participants performed worse than non-stressed SP participants whereas this effect was *not* present in the RP stress group – confirming stress impacts performance but dependent on the memorisation technique. Further, within the RP group, the stressed versus non-stressed participants showed no significant difference in performance on both the immediate and delayed testing. Finally, RP recall performance was higher than SP irrespective of stress or non-stress conditions, suggesting it is a better memorisation strategy on its own. The authors attribute the patterns on immediate *v*. delayed recall to two effects – immediate stress and noradrenaline facilitating recall, and the slower cortisol response inhibiting memory recall. Using an effective learning technique, memories can be protected from the effects of stress.

Would intranasal antipsychotics be a valuable addition to our repertoire of treatments? There's been very little development of this mechanism of delivery in psychiatry – recent oxytocin studies being a notable exception – though it's not uncommon in other branches of medicine. Katare *et al*[11] provide an update on the field. The method offers several potential benefits for anti-psychotics. Rapid absorption means that they can attain plasma levels at a rate similar to intravenous administration; they avoid gastro-intestinal enzymatic degradation and first-pass metabolism, with greater bioavailability meaning that lower doses and reduced side-effects may be possible; and some patients have difficulty swallowing tablets but dislike injections. Further, as well as absorption into the blood stream and thence systemic circulation, the nasal cavity also offers a *direct* pathway into the brain through the terminations of the olfactory and trigeminal nerves that circumvents the blood–brain barrier. However, there are issues about the volume of deliverable drug, many compounds are inadequately soluble for this method, and there are potential challenges around tolerability and irritation. Experimental animal studies have shown that it is feasible to attain appropriate pharmacokinetic and pharmacodynamic profiles for antipsychotics, and indeed that nanoparticles and nanoemulsions can be utilised to enhance delivery to the brain. Human studies are needed, and more data are required on potential toxicity. Perhaps not to be sniffed at, just yet.

Finally, selective reporting of data has been the bane of many pharmacotherapy trials; are psychotherapy ones doing things any better? Potential problems include publication bias, with journals favouring 'positive' results; researcher allegiance to a tested intervention; and selective reporting, whereby only statistically significant findings are reported. The OpenTrials collaboration is a very welcome development (http://opentrials.net/), but the focus typically remains on medications. Bradley *et al*[12] evaluated randomised controlled psychotherapy trials published between 2010 and 2014 in the five clinical psychology journals with the highest impact factors, identifying 112 studies. Just under 60% were registered (24% prospectively so), and only 11.6% (13 trials) were both correctly registered and reported. Of those 13 trials, seven had evidence of selective outcome reporting (four having discrepancies favouring significant outcomes), and overall, only 4.5% of trials were free from selective outcome reporting. There is currently no easy mechanism for verifying that data are analysed without bias in the majority of trials reported in the highest-impact journals, considerably affecting confidence in their findings. Transparency is needed across all interventional studies.

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