

## Kaleidoscope

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**Tell your story...a challenging prospect if you are a vulnerable refugee.** Sadly, there are an estimated 68 million people worldwide who have been forcibly displaced by war and persecution. Rates of post-traumatic stress disorder (PTSD) are notably high in refugee groups, but rates of seeking and obtaining care are low. Various factors contribute: from stigma about mental illness and fear of authority figures, through cultural and linguistic barriers, to suffering direct and indirect discrimination. Nickerson et al report on a randomised controlled trial to reduce stigma and enhance help-seeking, in over 100 men seeking asylum in Australia, all with PTSD symptomatology.<sup>1</sup> Participants either undertook an 11-module online ‘Tell your story’ (TYS) intervention, or stayed on a waiting list control group. All undertook assessments on stigma, PTSD symptomatology and help-seeking intentions at baseline, on completion of the intervention (or control) and 1 month subsequently. The 11 modules took participants through a stepped process about their personal journey, in topics such as ‘surviving stress’ and ‘how can talking help?’ Those in the YYS group showed significant reductions in stigma and increases in help-seeking behaviour. The whole principle is remarkably simple, and – dare we say it – obvious; its online nature makes it easily scalable. Could this narrative approach provide an accessible avenue to assist some of society’s most vulnerable individuals to access the care they deserve?

**Mood instability is often associated with emotionally unstable personality disorder, but it has wider resonance.** Taquet et al introduce a new concept, ‘mood homeostasis’: this is the stabilisation of one’s mood via engagement with mood-changing activities.<sup>2</sup> It is linked with what is known as the ‘hedonic flexibility principle’: when our moods dip, we engage in more mood-enhancing activities (sports etc), and conversely, when our moods are up, we are more likely to choose mood decreasing – but still useful (cultural etc) – activities. At least that is the theory for the population at large. Here they examined people with baseline low or high mood, and those with or without a history of a depressive disorder, tapping into the 58sec data-set of 60 000 individuals from low-, medium- and high-income economies.

They found mood homeostasis was significantly lower in those with a low mood and in those with a history of depression. Indeed, in that latter group, those with past episodes of depression showed no evidence of any mood homeostasis. Interestingly, in other groups, although the effect size of any given activity was small, these were cumulative, so multiple activities could help. The model estimated that lower mood homeostasis predicted more depressive episodes, and typically of greater duration. The inability to stabilise one’s mood through everyday activities is associated with worse outcomes; does it suggest any potential therapeutic avenues? The authors suggest that identification of lower homeostasis may indicate those at greater risk of depression, and also offer an intervention. They note how it might better inform ‘activity scheduling’ where patients map their planned activities with their therapist, aiming to avoid consecutive scheduling of unpleasant tasks.

**‘With mankind some expressions, such as the bristling of the hair under the influence of extreme terror, or the uncovering of the teeth under that of furious rage, can hardly be understood, except on the belief that man once existed in a much lower and**

**animal-like condition’** wrote Darwin on page 12 of the popular wedding-gift *The Expression of the Emotions in Man and Animals*.<sup>3</sup> As in so many areas of science, the mediating neurobiology between an internal state (for example sadness) and its external expression (for example facial expression) are often opaque. Dolensek et al take on this challenge in mice where they devised a battery of chemical and mechanical stimuli that tentatively correspond to evoked internal states: (a) oral quinine to provoke disgust, (b) oral sucrose for pleasure, (c) tail shock for pain, (d) lithium chloride injections for malaise, (e) escape for active fear, and (f) freezing for passive fear.<sup>4</sup>

They head-fixed and video recorded mice before, during and after experiencing these stimuli, which enabled them to process the video frames using a machine vision technique (histogram of oriented gradients (HOG)) to derive a numerical prototype that described the facial expression corresponding to each emotional state. Remarkably, the HOG-based emotion prototypes seem to capture and discriminate most of the different facial expressions (corresponding to the emotional states) in a species that appear to display very little discernible emotion (or at least it suits Kaleidoscope authors who have had to set mouse-traps to believe this). By repeating the experiment with different stimuli magnitudes (for example a softer or more vigorous tail shock) each facial expression followed a gradient – towards or away from the prototype – proportional to the magnitude of the stimuli presented.

Although this established the repeatability of stimulus-provoked facial expressions, it does not speak to the internal, mediating neurobiology. Using optogenetic stimulation, Dolensek et al directly stimulated three areas in the insular cortex and repeated the recording of facial expressions. While stimulating the anterior insular cortex, facial expressions most closely matched the ‘pleasure’ prototype. For the posterior insular cortex, facial expressions matched with disgust. Given the complexity of the insular cortex, they then tried to identify neurons that respond to a sensory stimulus, a change in facial expression or both. In the posterior insular cortex, they located cells that displayed activity correlating with facial expression (and changes in facial expression) and their segregation from those, which coded purely for stimuli evoking the putative emotional response.

**‘You’ve got to know when to hold ’em, know when to fold ’em’ taught the late Kenny Rogers (in relation to playing cards – not napkins at his excellent Kenny Rogers Roasters restaurants).** The US National Institute of Mental Health’s (NIMH) New Experimental Medicine Studies: Fast Fail Trials Program seeks to address slow psychiatric drug development by modifying early-phase studies, which, as currently structured, are notoriously likely to lead to the pursuit of high-cost failure in large-scale phase III trials. The lynchpin is the inclusion of biomarker-based proof of mechanism (POM) testing, more quickly eliminating drugs that will ultimately fail to achieve approval for their clinical indication. Additionally, the fast-fail approach encourages use of the NIMH Research Domain Criteria Project framework, a neurobiological structure for understanding psychiatric disease, rather than the DSM. Taken together, this neuroscience-centred approach focuses the trial on whether the target of interest has the intended neural impact, decreasing the likelihood of non-specific or indirect effects and making any phase III negative results interpretable and of value to advancing understanding of the mechanism’s contribution to clinical conditions.

Krystal et al delivered the first report to utilise this, investigating  $\kappa$ -opioid receptor (KOR) antagonism as a treatment for anhedonia.<sup>5</sup> Anhedonia transcends diagnoses presenting across several mood and medical conditions as well as numerous reward-related constructs. Preclinical data strongly suggest KOR antagonism in the

ventral striatum as a viable target for releasing the dopamine inhibition downstream, improving reward-related systems functioning, and potentially ameliorating anhedonia. Using a selective KOR antagonist (JNJ-67953964, previously CERC-501 and LY2456302) in a double-blind placebo-controlled trial, 89 participants showing prominent anhedonia were tested via functional magnetic resonance imaging and reward anticipation tasks, at both baseline and the conclusion of the 8-week regimen. Meeting the POM criteria, selective KOR antagonism was associated with higher activity in the ventral striatum and an improvement in anhedonia symptoms across the range of mood disorders. The magnitudes seen were consistent with the fast-fail hypothesis of mechanistic biomarkers having greater effect sizes than the clinical and behavioural measures, making them well suited for inclusion in these smaller trials. Taken together, these data provide a strong basis for both the pursuit of further investigation into KOR antagonism as an anhedonia therapy and a further phase III trial to verify the utility of this fast-fail approach in drug development. Although not the genetics-based avenue we have come to anticipate, this fast-fail POM approach holds the promise of delivering a different kind of precision medicine for psychiatry.

**Finally: what is the point of dads? Cheesy jokes, bad dancing, cringe-worthy speeches. Surely evolution should have got rid of them by now?** Certainly other primates do not have fatherhood in the same way. Evolutionary theory had previously worked on a model of a 'hired gun' who could provide protection and food to a female vulnerable with a child (known as paternal provisioning) – in exchange for sex. A problem with this, known as the 'social dilemma', is that competing with dads are...cads. A cad, who focuses on promiscuous mating and then leaving, is likely at an evolutionary advantage as he should sire more children, thus continuing his rogue genes. The counter was that females would reward long-term male care provision with sexual fidelity, denying this to cads. Nice theory, but it has problems, including the obvious fact that well, dad could end up looking after cad's children, so-called 'paternity theft'. And a quick comparison with promiscuous polygynous chimpanzee society shows none of this works there: rank and aggression, not providing bananas, are what gets the ladies in chimp-town.

Alger et al used game theory to propose a new solution – complementarities.<sup>6</sup> This is the division of labour and pooling of resources that create synergies between a couple, and which

cannot occur when each operates alone, including in hunter–gathering food accumulation. The fit that occurs in such partnerships optimises the strengths of each in providing for each other, far stronger than can occur in other modelled couplings. The foods obtained by the hunting male were nutritionally different (and complementary) to those captured by the gathering female; each could begin to specialise, but could not succeed without its mate. This appears to have begun between five and eight million years ago in early hominins, likely coinciding with ecological changes in Africa. At that time a drying of the landscape made sourcing energetically rich food more challenging, supporting adaptations that maximised resources – including long-term pair partnerships. What is perhaps strongest about this model is that it simultaneously allows cads to exist (a phenomenon that will surprise none), but they do not become dominant over dads. A tipping point is reached where dads' synergistic partnerships with mums lead to more offspring surviving to have their own children, and thus retention of the dad genes. So here's to plaid trousers, barbecue chefs and lost drivers who will not ask for directions – hurray for dads.

## References

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