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Kaleidoscope

Derek K. Tracy, Dan W. Joyce, Sukhwinder S. Shergill, Dawn N. Albertson

This month's Highlights column (A3) notes a reversing of clinical emphasis to sociopsychobio, but we never fully escape biology: why do psychoses persist? Given the young age of onset and the often-devastating impact on social interaction, presumably they should face significant negative evolutionary pressures. Previous Kaleidoscopes have described genetic links with creativity and early hominin language development; Mike Owen, in the Royal Society of Medicine's 2019 Darwin lecture, explained that new mutations continue to arise that will predispose to schizophrenia. Taking an evolutionary perspective, van den Heuvel *et al* contrast neuroimaging connectome data between homo sapiens and chimpanzee, and the changes observed in schizophrenia.[1] They found that the evolutionary advancements in human brain connectivity significantly overlap with the regions of dysconnectivity seen in schizophrenia, an effect not observed in other, less species-specific, mental illnesses – such as depression. These core regions are involved in semantic comprehension, language processing, cognitive control, social cognition, emotional processing and affiliative behaviour: all functions, the authors note, which can be disrupted in psychoses. It is the connections found only in sapiens that are most associated with problems in schizophrenia. Our enriched, specialised brain connectivity, the most complex parts that literally make us human, are those that predispose us to psychosis. For more evolutionary perspectives we commend Riadh Abed's discussions on outgroup intolerance theory[2] and the writings of Randy Nesse.[3]

Cannabis-derived medicinal products are attracting enormous public debate. In the UK and globally, legislative changes are moving towards greater access, but what is their scientific evidence? A systematic review and meta-analysis of the data of all cannabis formulations for mental disorders identified 83 studies: of these 42 looked at depression (23 randomised controlled trials (RCTs)), 31 at anxiety (17 RCTs), 8 at Tourette syndrome (2 RCTs) and 11 at psychosis (6 RCTs).[4] Pharmaceutical tetrahydrocannabinol (THC) improved anxiety in those with medical conditions (mainly chronic pain and multiple sclerosis) with or without cannabidiol (CBD), although the quality of the evidence was considered very low. THC, with or without CBD, worsened negative symptoms of psychosis, and no other effects were seen on mental illnesses. There were two notable conclusions: the evidence base is poor, so we might have an absence of evidence rather than evidence of absence; and there were few data on pharmaceutical CBD or medicinal cannabis. Perhaps most interesting is the surrounding debate, and the peculiarly unique societal position that cannabis occupies: it often splits people into those who see largely benign impact and benefit, and those who see it through the lens of harm. In both cases views often depart from the evidence.

'Major tranquillisers' is a historic name for antipsychotics but is sometimes used contemporaneously as a criticism that they only 'work' through sedation. Further, RCTs that compare antipsychotics with placebo face the challenge that side-effects might unmask participants to which intervention they are receiving, potentially skewing results in favour of the active treatment. One approach to overcome this criticism is to use active compounds in the control arm. A meta-analysis of RCTs comparing antipsychotics with barbiturates or benzodiazepines in the acute treatment of schizophrenia demonstrated that antipsychotics were significantly more effective than barbiturates, but there were inadequate data on benzodiazepines to draw any firm conclusions.[5] The findings rebut the challenge that effectiveness is a result of sedation or unmasking, although it is notable that the studies included are somewhat dated; a large contemporary RCT comparing antipsychotics with benzodiazepines would be interesting.

Physical interventions in psychiatry have a poor history, a shadow that hangs heavily over electroconvulsive therapy and, more recently, transcranial magnetic stimulation. This needs to be balanced against the burden of untreated and partially treated mental illness, not fully responding to medication or psychological intervention. One such novel target is the stellate ganglion that is situated in the neck and that mediates sympathetic nervous outflow; it has been used to successfully modulate symptoms in Raynaud's, hyperhidrosis and regional pain syndrome. However, excess and problematic sympathetic function is also notable in some mental illness, with post-traumatic stress disorder (PTSD) prominent in this regard. The first multisite RCT of stellate ganglion block on outcomes in PTSD reported a significantly superior improvement in symptoms in the active treatment arm; gains were greatest in those with the more severe initial symptomatology.[6] The 8-week follow-up duration was short, but there are enough data to warrant further exploration on effectiveness and any optimal treatment parameters. The participants had either paired right-sided stellate ganglion block via the anaesthetic ropivacaine, or a sham surgical procedure (a saline injection) at weeks 0 and 2; although one can speculate about mechanisms of action through dysfunctional feedback loops, the precise mechanism remain uncertain.

Predicting response to antidepressants remains a mystery. Major depressive disorder (MDD) is associated with impaired connectivity between brain networks that underlie cognitive, emotional and self-reflective processes. Using a practical clinical trial design, Korgaonkar and colleagues performed a connectome-wide analysis using functional magnetic resonance imaging to examine functional connectivity before and after treatment with first-line antidepressants.[7] Patients with MDD, either antidepressant naive or on a minimum 5 half-life washout period, received sertraline, escitalopram or venlafaxine-extended release for 8 weeks. At baseline, all participants with depression showed lower connectivity compared with control. However, those with an overall greater level of connectivity for their cohort, particularly in areas associated with awareness of self and cognitive control – the default mode network – were most likely to achieve acute remission at 8 weeks. This occurred regardless of the medication assigned and suggested that elevated baseline connectivity was not only predictive of acute remission, but perhaps also necessary for broad antidepressant action. This signature holds the potential to be a prognostic marker for treatment success, but also indicates a potential avenue for more directly targeted intervention in this network to augment antidepressant effects.

The artificial intelligence/machine learning 'hype-cycle' continues with the NHSX artificial intelligence lab initiative being recently funded to the tune of 250 million pounds.[8] The Topol review proposed benefit from such technologies,[9] largely motivated by previous successes in areas that are considered low-hanging fruit for machine learning techniques – for example, deep learning applied to radiological image interpretation. Time will tell how these specific exemplars generalise to other medical decision-support domains, but specifically of interest to psychiatry, and society more generally, is the prediction of future suicide. To date, empirical studies of the performance of risk scales inform us that these tools perform poorly. Current guidance from the National Collaborating Centre for

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Mental Health advises against reliance on risk assessment tools to predict suicide or self-harm instead emphasising knowledge of risk factors to motivate effective planning for intervention and care provision. There has been an increase in the literature using clinical records, social media as well as more biometrically informed methods (such as speech pattern recognition) to make predictions for suicide risk.

A recent paper provides an interesting viewpoint in combining different sources of data at different points;[10] they identify that the positive predictive value of automated tools is poor for the vital task of identifying high risk of suicide (not least because the prevalence of suicide is low) but that the same systems are generally better for predicting lower risk of suicide. So instead of hoping for a 'one-shot' assessment of prediction for suicide, they suggest that these tools might be better used for triaging and directing patients into a three-stage clinical assessment pathway. Kessler *et al* suggest that the first stage might screen-out patients using predictive models derived from administrative or demographic data from, for example, structured data in electronic health records. The second stage might be administration of standardised assessments including self-report risk scales; the argument is that there is a benefit of reporting stigmatising or embarrassing thoughts and behaviours using tools that do not require disclosure directly to a clinician. This second stage then directs patients to a third stage – the thorough, in-person clinical assessment directed towards those at higher risk. Importantly, Kessler *et al* review the principle of net benefit and decision-curve analysis as an alternative to the traditional presentation – that is in terms of sensitivity, specificity and positive predictive value. Decision-curve analysis allows a balance of direct and indirect costs when setting a threshold for a tool that detects or triages individuals at risk of suicide. For example, the three-stage process outlined above has direct (clinician time in stages two and three as well as the intervention cost) and indirect costs (intrusive or coercive input to a patient's care pathway). Instead of dismissing suicide risk prediction based on the existing tools having low positive predictive value, they argue that we do not have the necessary information to derive the net benefit and decision-curve analyses to evaluate these prediction systems.

Finally, Billy Ray Cyrus hollered 'don't tell my heart, my achy breaky heart, I just don't think he'd understand', in the process achieving the first ever triple platinum single in Australia. As well as confirming the excellent musical tastes of our antipodean friends, in using the word 'he' Billy Ray mysteriously but appropriately hints at gender differences in heart break. Does this translate to variation in how we view our ex-relationships? Recent research suggests yes,[11] arguing that from an evolutionary viewpoint women typically invest greater energy and resource into offspring, and thus have more 'pragmatic' views on love (their word), with stronger preferences for longer-term exclusive relationships. Conversely, men are more likely to endorse a 'game-playing' attitude to love (again, their phrase: you might have your own choice alternative), aimed at maximising sexual contacts. It has been observed that men are typically more dependent on their partners for emotional and practical needs; women tend to blame men for break-ups rather than the other way round; and post-break-up coping strategies are more often emotional support or positive self-talk in women and distraction in excess work or sports for men.

The work of Athenstaedt *et al* covered 900 individual's responses; so, what were the findings? It confirmed that men view their ex-partners more favourably than women. In accordance with sociological perspectives, having a more permissive sexual attitude and social support from an ex – things typically higher in men – enhanced such views; attributing greater blame on the break-up to the ex – typically higher in women – decreased them. We'll let y'all sign off singing along with Billy Ray: 'and if you tell my heart, my achy breaky heart, he might blow up and kill this man'.

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