

## Kaleidoscope

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

**There are ongoing concerns about the impact of antipsychotic use during pregnancy, particularly with respect to increased risks of neurodevelopmental complications.** There are few randomised controlled trials in pregnant women, and there is the major confounder that the condition being treated may itself be associated with adverse effects in the infant. Wang et al<sup>1</sup> used a population-based cohort observational study of almost half a million mother-child pairs in Hong Kong, measured across a 14 year timeframe. Subsequently, just over 13 000 children were diagnosed with attention-deficit hyperactivity disorder (ADHD) and just under 9000 with an autism spectrum disorder (ASD). A sibling-matched analysis was included to try to account for unmeasured genetic and environmental confounders, and women concomitantly prescribed antidepressants or lithium were excluded owing to a recognised association with the adverse outcomes under evaluation. Analysis of gestational exposure to antipsychotics, whether first- or second-generation medications, found no association with either condition, or indeed with preterm birth or babies being small for gestational age. There is an association between maternal mental illness and higher rates of children developing ADHD and ASD, but the prescribed antipsychotic medications are not driving it (this is an example of confounding by indication). Here, the benefit/risk ratio for treatment during pregnancy is weighted far more towards active pharmacological intervention. The findings are important and should be a source of reassurance to many patients and clinicians.

**The complex genetics of mental illnesses, along with their impact on the brain, are gradually being unwrapped: what update in schizophrenia?** This is recognised to be up to 80% heritable, but thus far it has proved troublesome to link risk genes to subsequent structural changes in the brain. Traditionally, the suggestion has been that this is due to inadequate sample sizes, particularly from neuroimaging studies, and that most such work inevitably prioritises larger-scale morphologies such as grey matter volume and surface area. A recent genome-wide association study determined 270 risk loci, from which a polygenic risk score (PRS) can be created that accounts for a little under 10% of the variance in the disorder. Stauffer et al<sup>2</sup> applied this to a very large data-set of almost 70 000 patients and a quarter of a million controls to measure the PRS for the near 30 000 adults in the UK biobank who had been genotyped and had a range of magnetic resonance imaging (MRI) measurements. They then explored for associations with micro and macro changes on the brain scans. Polygenic risk was linked with a reduction in neurite density index (NDI) across the whole brain, in a range of cortical and subcortical regions, as well as white matter tracts ('neurites' are constituted by dendrites and axons). There was preliminary support for a *causal* relationship between reduced NDI in the thalamus and a greater risk of illness. The findings suggest that decreased dendritic arborisation and density of myelinated axons, and the emergent dysconnectivity in cortico-subcortical networks, might be the genetic mechanism through which psychotic illness ultimately emerges.

**'The function, the very serious function of racism is distraction. It keeps you from doing your work. It keeps you explaining, over and over again, your reason for being' taught Toni Morrison.** She speaks to the conditions created by racism that demand defence by

global majority populations over and over again, taking up time and resources so the real work of dismantling racist structures cannot be accomplished. In an interesting connection, this parallels what is seen in the brain. In addition to the injurious impact on mental and physical health that is well known, racial discrimination activates a heightened threat vigilance that drains cognitive reserve and impairs performance on attentional and executive function tasks. Additive experiences of racism are theorised to have a kindling effect that sets off chronic hyperactivation of the hypothalamic-pituitary axis and increases vulnerability to poor health outcomes, but discrimination-related neurocircuitry has been largely ignored. Negar Fani and colleagues<sup>3</sup> recently identified the brain response patterns, expected mediators of long-term outcomes, to emotionally salient cues in trauma-exposed US Black women. Controlling for post-traumatic stress disorder (PTSD) and non-racial trauma exposure, experiences of racial discrimination were negatively correlated with performance on trauma-relevant stimuli during the affective Stroop task. Even with a conservative whole-brain correction applied, functional MRI imaging showed strong reactivity in visual attention, emotional regulation, and fear inhibition areas including the ventromedial prefrontal cortex (vmPFC). The vmPFC is known to be associated with PTSD symptomatology, so its involvement indicates a race-specific impact on this regulatory area. While the vmPFC activation may contribute to the harm done via biological stress systems, it may also be a marker of resilience and adaptive threat response. These interesting possibilities beg for additional studies across wider groups on the neural effects of suffering discrimination, including investigating individual differences. Following this thread, clarifying the pathways involved in race-related health disparities will be key to understanding the physical damage done by racism, as experienced by the overwhelming majority of people in communities of colour.

**Reducing criminal recidivism is important for society; while modifying the social drivers of poverty and disadvantage are key, what opportunity is there for psychological interventions?** Between a third and half of those released from prison will reoffend within a few years, at considerable personal and societal cost. Some trials of cognitive-behavioural therapy (CBT) have shown that this can be reduced by about a quarter, but the literature is notably heterogeneous. Beaudry et al<sup>4</sup> performed a meta-analysis of 29 randomised controlled trials, which included almost 10 000 participants (12% women). Initial analysis of the pooled data supported the effectiveness of CBT in reducing recidivism, but when smaller trials of fewer than 50 participants were removed, this positive effect was no longer observed. Such programmes are relatively widely utilised across prisons. These data do not support their use and indicate that publication bias and small-study effects have led to overestimation of their impact. The authors note some interesting supportive data for the specific intervention of therapeutic communities, but this was based on just two studies. It is noteworthy that the CBT interventions have not classically been allied with psychosocial support around employment, finances and accommodation upon release from prison; moreover, they have largely just been modifications of community-based approaches rather than being personalised for this group. The paper concludes that new treatments should perhaps focus more on modifiable reoffending risk factors.

**Artificial intelligence and machine learning (AI/ML) have yet to live up to the hype in psychiatry: what's gone wrong, and where might change come from?** A guide to evaluating machine learning by Grzenda et al<sup>5</sup> focuses on the pipeline between possessing some data and building and evaluating a model. Almost all AI/ML methods automate the discovery of a model that maps inputs to

outputs (e.g. symptoms to a diagnosis). They describe the dominant ‘paradigms’ such as supervised, unsupervised and reinforcement learning, and survey natural language processing methods and the use of electronic health records. Examples are provided for the busy, non-expert clinician of how to evaluate the claims and reporting in the literature. Importantly, they provide a readable guide to bias–variance trade-off (avoiding shoddy performance when an algorithm over-simplifies things versus exceptional performance arising as an artefact of very complex models overfitting to data). Throughout, the authors emphasise clinical considerations as they relate to the technology – especially data pre-processing and the evaluation of model performance. For reasons of brevity, they perhaps rely too heavily on assurances that cross-validation offers a ‘good estimate of how the model will perform on completely new data’ and they don’t consider cross-validation in the context of the superfamily of resampling methods and efficiency trade-offs. This is important because the AI/ML healthcare field moves rapidly, and high-profile claims of success are rarely followed up with prospective and *external* validation, where a predictive model’s performance is demonstrated in data demonstrably separated from those on which it was trained.

Grzenda et al are careful to conclude their paper with important ‘buyer beware’ messages: model transparency and explainability, and algorithmic fairness and healthcare justice. With huge models, containing hundreds to thousands of predictor/feature variables, directly understanding how inputs are influencing output predictions is not possible. Contrast this with familiar regression models, where we can directly interpret the effect each predictor has on the model output. Predictive models of the former kind are so hard to interpret that we need to pay extra attention to ascertain they are *not* giving outputs biased against underrepresented or minority groups. It is noted that tools for AI/ML have become more user friendly, making the learning curve shallow; this benefits entry and experimentation but risks methodological error, similar to the case of easy-to-use and available statistical software contributing to the erroneous belief that a statistician is superfluous to analysis because anyone can operate these applications. There is a clear need to improve efficiency and outcomes for patients within our health system, and AI/ML will have a part to play in the future; understanding the pros and cons of these approaches is key. As Paul Meehl<sup>6</sup> put it, ‘Every hour spent in thinking and talking about *whom* to treat, and *how*, and *how long* is being subtracted from the available pool of therapeutic time itself.

**Finally, ‘mass sociogenic illnesses’ (MSI) have largely been relegated to the archives of history; however, a new paper reports a 21st century rebirth – ‘mass social media-induced illness’.** The backdrop is a young German man with Tourette syndrome, who has the second highest YouTube following in that country. Writing in *Brain*, Müller-Vahl et al<sup>7</sup> note that his videos confirm his diagnosis, but that many of his movements and vocalisations are bizarre, mimicking those a lay public might associate with this disorder. The authors describe them as ‘clearly functional in

nature. Tourette experts can easily tell the difference’, and they go on to note the discrepancies compared with ‘true Tourette’s’. The individual’s YouTube channel (<https://www.youtube.com/channel/UCh2Nc3OwjSwuXrUdFNXqFbQ>) has over two million subscribers, and his videos of his difficulties have been viewed over 300 million times (and have a merchandise link for t-shirts and caps). Fascinatingly, the authors, who run a specialised Tourette service, report that in the past 2 years, they have seen a remarkably high number of referrals of young people with symptoms resembling those seen in the videos including, for example, the exact same vocalisation ‘tic’ of ‘Fliegende Haie’ (‘flying sharks’) and the behaviour of crushing eggs in their kitchens. Again atypically, such difficulties often prevented sufferers from completing unpleasurable tasks, such as school obligations, and remitted when undertaking favourable activities. Rather than Tourette syndrome, such individuals are proposed to have a ‘Tourette-like’ functional movement disorder.

The authors write that they view this as a ‘21<sup>st</sup> century expression of a culture-bound stress reaction of our post-modern society emphasizing the uniqueness of individuals and valuing their alleged exceptionality, thus promoting attention-seeking behaviours and aggravating the permanent identity crisis of modern man’. We feel this is perhaps a little harsh, and we are reminded that, historically, MSI has often evoked a prurient, voyeuristic and dismissively patronising (often sexist) professional response: some of us might recall being taught about ‘dancing plagues’ in the Middle Ages or ‘outbreaks’ of bizarre fainting bouts in some schools. There can be little doubt that social media will affect many people in different ways, but clinical curiosity and empathy must always remain our starting points.

## References

- 1 Wang Z, Chan AYL, Coghill D, Ip P, Lau WCY, Simonoff E, et al. Association between prenatal exposure to antipsychotics and attention-deficit/hyperactivity disorder, autism spectrum disorder, preterm birth, and small for gestational age. *JAMA Intern Med* [Epub ahead of print] 16 Aug 2021. Available from: <https://doi.org/10.1001/jamainternmed.2021.4571>.
- 2 Stauffer E-M, Bethlehem RAI, Warrier V, Murray GK, Romero-Garcia R, Seidlitz J, et al. Grey and white matter microstructure is associated with polygenic risk for schizophrenia. *Mol Psychiatry* [Epub ahead of print] 30 Aug 2021. Available from: <https://doi.org/10.1038/s41380-021-01260-5>.
- 3 Fani N, Carter SE, Harnett NG, Ressler KJ, Bradley B. Association of racial discrimination with neural response to threat in Black women in the US exposed to trauma. *JAMA Psychiatry* 2021; **78**(9): 1005–12.
- 4 Beaudry G, Yu R, Perry AE, Fazel S. Effectiveness of psychological interventions in prison to reduce recidivism: a systematic review and meta-analysis of randomised controlled trials. *Lancet Psychiatry* 2021; **8**: 759–73.
- 5 Grzenda A, Kraguljac NV, McDonald WM, Nemeroff C, Torous J, Alpert JE, et al. Evaluating the machine learning literature: a primer and user’s guide for psychiatrists. *Am J Psychiatry* 2021; **178**(8): 715–29.
- 6 Meehl P. *Clinical versus Statistical Prediction*. University of Minnesota Press, 1954 (1996 reprint: Echo Point Books).
- 7 Müller-Vahl KR, Pisarenko A, Jakubovski E, Fremer C. Stop that! It’s not Tourette’s but a new type of mass sociogenic illness. *Brain* [Epub ahead of print] 23 Aug 2021. Available from: <https://doi.org/10.1093/brain/awab316>.