

Kaleidoscope

Derek K. Tracy, Dan W. Joyce,
Sukhwinder S. Shergill

'Be in me as the eternal moods of the bleak wind' wrote Ezra Pound. Laruelle & Abi-Dargham memorably provided us with psychiatry's version, calling dopamine **'the wind of the psychotic fire'**.¹ Does it blow transdiagnostically across both schizophrenia and bipolar affective disorder? This would fit with the popular dimensional view, but the nature of dopaminergic changes in these conditions have remained ambiguous. Using positron emission tomography Jauhar *et al*² found elevated striatal dopamine synthesis capacity in both clinical groups – with no differences between them, and a positive correlation with symptom severity – of individuals with a first episode of bipolar psychosis ($n=22$, 18 antipsychotic naive or currently drug free) or schizophrenia (16, with 14 drug-naïve), as well as 22 controls. Illness duration and use of medication did not impact the findings, which support the model of increased dopamine synthesis being a psychotic state rather than an illness trait. Patients were followed-up for a year and a half and diagnoses remained stable. The findings support a transdiagnostic role for dopamine in psychosis, strengthened by the large number of participants who were drug free or naïve. Current dopaminergic drugs work through post-synaptic receptor blockade; focusing on the core dysfunction in dopamine synthesis is proposed to offer a new target across both disorders.

Attention-deficit hyperactivity disorder (ADHD) is a growing issue for adult mental health, with both 'graduates' from children's services and the specific challenge of later-life diagnosis. A large proportion of the latter group are individuals realising they have long had an undiagnosed problem, often precipitated by seeing their own children receive help for similar difficulties, but there is a particular issue about late onset: can ADHD *start* in adulthood? This goes against the predominating model of ADHD as a chronic neurodevelopmental condition, although late onset is supported by data from birth-cohort studies. However, screening instruments often don't consider alternative causes, so Sibley *et al*³ explored eight longitudinal psychiatric assessments in each of 239 individuals from childhood (mean age 9) to young adulthood (24). As well as parent, teacher and self-reports of ADHD symptoms, diagnostic consideration was given to other symptoms, wider context, and onset timing. Astonishingly, 95% of those who screened positive for late-onset ADHD were excluded from the diagnosis – most commonly because ADHD symptoms occurred entirely with substance use – and there was no evidence for adult-onset ADHD independent of a complex psychiatric history. The authors conclude that there may be very few instances of true late-onset ADHD and caution that clinicians need to be very careful in exploring confounders during assessment, especially drug use. They invoke the so-called 'false positive paradox' of potentially transient things skewing much of the existing literature and 'ADHD' inappropriately becoming a catch-all diagnostic category.

The reproducibility, or replication, crisis as a major issue in science has received increased attention of late. An editorial by Monya Baker⁴ surveyed 1500 scientists to find that 52% agreed it was real, 20% had been contacted by others trying to reproduce their findings, while 24% and 13% of respondents had succeeded in publishing a successful or failed replication respectively. A

further *Nature* editorial⁵ discusses the impact of the journal's checklist mechanism for improving reporting transparency and addressing this 'crisis'. It discusses a review by Malcolm MacLeod *et al* of over 220 papers before and after the introduction of *Nature's* checklist, examining the following reporting standards: randomisation, exclusions, masking procedures, and sample-size calculations. Prior to the checklist's introduction in May 2013, the proportion reporting all four standards was zero, but rose to 16% after. Perhaps more pertinent than the result was that the MacLeod study was itself an exercise in transparency, demonstrating a full-cycle approach to publication. First, their review protocol was published in a peer-reviewed journal, allowing for critiquing the proposed methodology to reduce bias in their proposed review. They published a preprint on the bioRxiv service (<https://www.biorxiv.org/>) inviting community review before submission, and the analysis plan and code was published in advance on the Open Science Framework service (<https://osf.io/>). Finally, the complete data-set from the study was made public on Figshare (<https://figshare.com/>). The editorial concludes by discussing double-blind peer review as a way of removing bias in the publication process. The *Nature* journals have noted 9–14% uptake of double-blind reviewing since it was introduced in 2015. This is interesting, as it appears relatively novel in the biosciences – in contrast to other fields where it has been largely the norm for some time. Yuriy Brun – an academic software engineer and computer scientist – published a letter (<https://people.cs.umass.edu/~brun/doubleblind.html>) that outlines the positives of double-blind peer review, which include less bias from authors' institutional affiliation (mitigating against eminence-based publication) and increasing participation in publishing from underrepresented groups.

Deep brain stimulation (DBS) for depression is inevitably controversial. It intertwines historically regrettable associations of psychiatry with potentially worrying images of neurosurgery in vulnerable individuals. However, there is a genuine unmet need in the sunless cliffs of refractory illness and an ongoing search for novel interventions. There are plenty of interesting DBS pilot data and open-label case series, but a larger lack of methodologically sound work. Holtzheimer *et al*⁶ implanted 90 participants with treatment-resistant depression (TRD) with a DBS system targeting subcallosal white matter (Brodmann area 25, which has significant associations with TRD). What was impressive and atypical about this work was that they were then randomised to receive either active or sham stimulation for 6 months, and it was double-blinded, with clinical assessors measuring response rates also unaware of who was receiving the active intervention. Uptake of the study was aided by offering all participants 6 months of open-label DBS after the randomisation period. No significant improvements in response (>40% symptom reduction) were seen in the active group over placebo, and there were eight serious adverse events (in seven patients) directly attributable to the study device or surgery. An unanswered challenge in all such work is that ethically, it inevitably tends to be reserved for those whose illness is treatment resistant; furthermore, this particular study did not utilise tractography or intraoperative testing to evaluate localisation optimisation. The troubling and persistent questions in the grey waters of neuromodulation remain whether the techniques are not very good, not good in a particular cohort, or we're just not very good at optimising them: for now, our best data say DBS to the subcallosal cingulate does not work in TRD.

Adherence to antidepressant treatment is commonly low, and this is a particular problem in primary care, where 90% of patients are treated. The first 6 weeks of treatment have been

shown to be a particularly important time to ensure adherence, with greater vulnerabilities from discontinuation during this period. Older adults have been argued to be especially susceptible owing to various factors, including polypharmacy and differential beliefs about mental illness. Sirey *et al*⁷ tested the effectiveness of a psychosocial intervention to improve early adherence among older patients recently commenced on an antidepressant in this setting. Across three 30-minute sessions over a 6-week period, those randomised to the active group identified and addressed barriers to adherence, which included stigma and fears and misconceptions about being on medication. They were five times more likely to be adherent at 6 weeks than those randomised to treatment as usual (TAU) (and three times more so at 12 weeks) – an enormous difference clearly showing that psychoeducation works. Crucially, greater adherence to care was associated with greater improvements in depression (including in those receiving TAU).

Last month's Kaleidoscope argued that the nocebo effect did not explain antidepressant trial results.⁸ But nocebo is still a *thing*. Regarding pain, Brian Warner pondered 'When you want it, goes away too fast . . . times you hate it, always seems to last'. In masked trials of analgesics, the placebo effect is magnified when the intervention is presented as a more expensive medication; people know that generic medications are not inferior to their branded counterparts but, a bit like public transport, generally favour it for others rather than themselves. Medication colour affects perceived side-effects: blue and green tablets sedating, and red/orange ones (falsely) associated with stimulant effects. The nocebo effect is where participants get worse, or they report the expected negative side-effects from the placebo medication. However, there has been little focus on the nocebo effect being modulated by perceived value (expensive *v.* cheap) of a medication. Tinnermann *et al*⁹ used a novel functional magnetic resonance imaging (fMRI) protocol to simultaneously image the cortex, brain stem and spinal cord regions associated with pain perception and modulation alongside an expectation-induction paradigm to show how participants display larger nocebo effects when exposed to a topical cream in blue (expensive) rather than orange (cheap) packaging. An independent group were used to establish that the blue-boxed medication was valued as significantly more expensive than the orange-boxed version – but both 'medications' were in fact placebo for the actual experiment.

Forty-nine participants were randomly assigned to blue or orange nocebo and both groups were also exposed to a control condition (a third placebo cream, identical to the others, but without packaging/value information). In the induction phase of the experiment, after application of the cream to the forearm, the participants had the treated area stimulated with a heat-pain device. Covertly, the temperature was increased for the nocebo and decreased for the control cream to match the expectation that the expensive cream was 'more active'. In the test phase, participants were placed in the MRI scanner and this time, there was no difference in the heat applied to the treated forearm. Measurement of subjective pain was no different in the induction phase (where the temperature was deliberately altered). However, in the test phase people reported the expensive (blue) medication caused more pain than the orange (cheaper) medication. Repeated applications of the test procedure also showed that the nocebo effect was increased as time progressed, and this was not influenced by control conditions (i.e. no packaging value). The fMRI results showed that the periaqueductal grey (PAG) – a midbrain area which modulates ascending and descending pain pathways – responded

with greater activation differences between the expensive nocebo and control conditions when compared with cheap nocebo and control condition. In a mediation analysis, reduced activity in the right anterior cingulate cortex (rACC) was associated with reported increase in pain during nocebo treatments, suggesting an inhibitory function for cortical modulation of midbrain pain gateways. Patients in clinical trials commonly discontinue medication because of side-effects, and many of them are in the placebo arm – the nocebo response: these data illustrate how value information informs this.

Finally, we aim only to provide you with the best science, never to induce moral panic with clickbait headings. So, will violent videogames harm your children? Kaleidoscope previously dismissed so-called 'internet gaming disorder' as an unlikely novel addiction.¹⁰ However, there has been some work suggesting differential emotional and cognitive functioning in heavy users of violent computer games, though little unpicking of game content and exact quantity of play. Stockdale *et al*¹¹ use electroencephalography to measure neural correlates of response inhibition, and tested how these related to empathy in users of video games with very violent content. Heavier users had reduced empathy levels, as well as decreased brain activity detected by P100 and N200/P300 event related potentials during an affective stop-signal task that evaluated implicit attention to emotion and response inhibition. The inevitable reactive tabloid newspaper headlines in days hereafter write themselves, and just in time to impact your Christmas purchases. To further assist, we're going to field test for any differential effects between Wolfenstein II and Resident Evil 7, with Grand Theft Auto (part V, obviously) our baseline TAU. Merry Christmas.

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- 5 Nature. Steps towards transparency in research publishing. *Nature* 2017; **549**: 431.
- 6 Holtzheimer PE, Husain MM, Lisanby SH, Taylor SF, Whitworth LA, McClintock S, et al. Subcallosal cingulate deep brain stimulation for treatment-resistant depression: a multisite, randomised, sham-controlled trial. *Lancet Psychiatry* 2017; **11**: 839–49.
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- 8 Tracy DK, Joyce DW, Shergill SS. Kaleidoscope. *Br J Psychiatry* 2017; **211**: 327.
- 9 Tinnermann A, Geuter S, Sprenger C, Finsterbusch J, Büchel C. Interactions between brain and spinal cord mediate value effects in nocebo hyperalgesia. *Science* 2017; **358**: 105–8.
- 10 Tracy DK, Joyce DW, Shergill SS. Kaleidoscope. *Br J Psychiatry* 2017; **210**: 87–8.
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