

Kaleidoscope

Derek K. Tracy, Dawn N. Albertson, Anna Sri,
Sukhwinder S. Shergill

We continue to count the ongoing costs of COVID-19, with an increasing emphasis on ‘long covid’ and enduring systemic effects. Writing in *Nature*, Stein et al¹ undertook autopsies on 44 unvaccinated people who had died in the year to March 2021, including sampling multiple sites in the central nervous system. Their aim was to map the persistence, distribution, replication competence and cell-type specificity of any identified virus in individuals whose time of death varied from shortly after infection to 7 months later. The patterns differed across those sampled, but the virus was widely distributed in their bodies, including in non-respiratory tissue, and it was often present in the brain, even early in infection. The systemic distribution was greater in those who had died with severe COVID-19, and it was noteworthy that there was persistent viral RNA in brain tissue up to 230 days after initial symptomatology. Fascinatingly, and perhaps somewhat concerning, there was little evidence of inflammation or direct viral cytopathology beyond the respiratory tract despite the ongoing presence of the virus. The authors posit that there might be altered interferon signalling or disrupted antigen processing and presentation, and subsequently less efficient viral clearance in extra-respiratory tissue. This may have important implications for future therapeutics aimed at facilitating viral clearance. In this still rapidly moving environment, not least with continuing virus mutations and varying population patterns and numbers of those vaccinated and having had boosters, the authors express some caution in how broad our inferences from their findings should be. Some of those sampled had relatively early forms of the disease, and they were all unvaccinated and older, and died with it, so they clearly do not necessarily fully represent global populations in 2023.

When it comes to motivation to exercise, the psychology is better understood than the biology, but that is changing. Dohnalova et al² report on a novel microbiome-dependent gut–brain pathway that appears to regulate motivation for exercise – at least in mice. The authors took a cohort of genomically well-profiled mice with a wide variability of baseline treadmill and wheel running. They then examined genome-wide association and non-genetic factors, the latter including serum metabolomes, intestinal metabolic parameters and microbiome composition. The inclusion of the last of these was based on emerging work suggesting a gut influence on exercise performance, though any mechanism and its relative importance have been unclear. Here, the genetic contribution to exercise was low, implying that other aspects had greater roles. The authors discovered that synthesis of endocannabinoid metabolites in the gastrointestinal tract stimulated the activity of a specific subtype of sensory neuron – TRPV1 – which in turn promoted the downregulation of MAO expression in the ventral striatum and subsequently increased dopamine levels during exercise. Stimulation of this pathway, including through microbiome transplantation, enhanced the running performance of the mice, whereas blockage of it through microbiome depletion via antibiotics, spinal ablation or dopamine blockade reduced performance. Without the microbiome, the exercise-induced dopaminergic surge was blunted, and this seems to be key to motivation and performance. Clever application of specific antibiotics allowed determination of key roles for members of the Erysipelotrichaceae and Lachnospiraceae bacterial families. The authors hypothesise that the evolutionary underpinning is the regulation of exercise drive and reward by nutrient availability, telegraphed by gut microbes.

Conversely, anorexia nervosa is associated with hyperactivity, as well as reduced food intake, as part of weight reduction. Once again turning to mouse models, the rodent analogue of ‘activity-based anorexia’ (ABA) can be induced by placing the mice on a running wheel and restricting access to food. Sutton Hickey et al³ evaluated the hypothalamic neurons of mice in such a paradigm, focusing on agouti-related peptide (AgRP); this peptide has established links to regulation of appetite by promoting hunger and food-seeking, but its function has been less well delineated in the context of hyperactivity, which is present in about 80% of anorexia nervosa patients. They found that ABA development in mice could be mitigated by chemogenetic AgRP activation that occurred by reprioritising increasing meal numbers over hyperactivity when food was available. These studies suggest potential for pharmacotherapeutics: first, through interoceptomimetic compounds to replicate the transmission of GI signalling and enhance exercise motivation in humans; and second, through potential targeted approaches to reduce behavioural maladaptations commonly seen in anorexia nervosa.

Many of us working in mental health wince when we hear media chatter about the need for better psychiatric evaluations following a mass murder, and the mention of ‘madness’ and delusions. But what’s the evidence on the topic? This is clearly relevant in terms of the impact on policy, and mass murders (typically defined as killing four or more individuals) are not limited to the infamous shootings that seem commonly reported in the media. Brucato et al⁴ explored global data, including demographics of the perpetrators, from 1900 to 2019 that covered approximately 15 000 murders and looked at any variations in the subgroup of the 1315 mass murders. Sixty-five per cent of mass killings involved firearms, and among such perpetrators 8% had a lifetime history of a psychotic illness, which is *less* than the rate in non-mass murderers (we know, what a peculiar term and relative concept). Those who committed mass shootings in the US were far *more* likely to have previous legal problems, substance misuse difficulties and a non-psychotic illness. Once again, most people with psychosis are neither dangerous nor violent, and most violence is committed by those without mental illness. This is not to ignore the fact that there are clearly instances of illness-driven (particularly psychosis-driven) violence, and mental health services have clear obligations in risk assessment and management. However, the authors correctly conclude that policies to reduce such horrific events are best aimed at tackling issues other than serious mental illness; trying to better manage substance use and reducing access to firearms are proposed as the ways forward. How palatable that is to politicians remains to be seen.

Moving to where we do need more resources: there have been persisting mental health inequalities among LGBTQ+ groups compared with their heterosexual peers. In the UK, sexuality is protected under the Equality Act, yet LGBTQ+ individuals frequently face prejudice and discrimination. What’s evident is that along with homophobia, bullying and hate crime, as well as commonly social marginalisation, mental health inequalities persist, and it’s argued that our LGBTQ+ communities aren’t receiving equitable mental health support. Pitman et al⁵ show that the UK mental health inequity gap with heterosexual groups persisted between 2007 and 2014 without any reduction, adding that bisexuals experience poorer mental health than other sexual identity groups. A real strength of this work was its random sampling from a large nationally representative longitudinal study. The authors note that LGBTQ+ patients are just not adequately visible in the healthcare system, with a lack of awareness from too many professionals. As a result, many feel unable and unlikely to disclose

their sexual orientation, exacerbating difficulties in receiving timely treatment and support. The authors make clinical and policy recommendations, such as positive images of LGBTQ+ individuals in health service marketing materials, the display of equal opportunities with respect to the groups of sexual orientation and an LGBTQ+-affirmative stance in psychotherapy. In 2020, routine monitoring of sexuality in mental healthcare services became mandatory in the UK, assisting auditing of service provision and changes over time. There is a question of how far we might have advanced since 2014, with the caveat that the pandemic seemed to exacerbate inequalities. That many in LGBTQ+ communities don't feel secure enough to fully disclose their sexual orientation when seeking rightful healthcare speaks loudly, and we need to hear this. This is both a public health issue and a human rights issue, and it is everyone's business whatever their sexual orientation.

Though psychiatry is firmly intertwined with neuroscience, the study of the mind has roots in philosophy. Whereas Descartes articulated the mind and body as separate entities, psychology truly emerged as a discipline once the physiologist Wilhelm Wundt began to apply experimental methodologies to our internal mental processes. In the beginning there was room for intangible, subjective experiences, but soon after, a prioritisation of observable phenomena took hold. In many ways, this staunchly objective approach has proven to be fertile ground for advancement. This is exemplified in the development of the DSM, which provided a universal framework for clinicians by articulating observable criteria for diagnosis and categorisation. In that time, rather than coming closer to a unified understanding of the physical and subjective aspects of the mind, biological conceptions have come to dominate. In parallel, Evan Kyzar and George Denfield at Columbia University argue⁶ that our research and understanding of psychiatric illness have been limited by the implicit biases that have resulted. They posit going back to our philosophical roots in order to move forward. They argue that welcoming phenomenology – the study of subjective lived experiences – will help tease out that which is often missed with our current approach and, in doing so, will give us not only a richer understanding of psychiatric illnesses but will provide novel targets for biological investigation. The authors propose adopting a neurophenomenology framework, or the investigation of first-person subjective experience narratives via objective neuroscience techniques, to move the field forward. Instead of structured diagnostic interviews, phenomenological psychiatrists would use semi-structured interviews and qualitative research methods to identify themes both within and across diagnoses. Taken within the context of what is known about the biological underpinnings, these phenomenological themes or clusters would provide testable hypotheses for computational and neuroscientific methods to look for patterns otherwise not seen. The neural processes behind these could be further investigated within preclinical models and across species. The authors present the process as a cycle of continual refinement of hypotheses between the clinical and preclinical domains – a conversation. The proposal is a modest one: better informed understanding of psychiatric phenomena by recentring the phenomena themselves. Rather than supplanting our biological methods, the inclusion of phenomenology in psychiatric research offers the potential to more effectively ask questions and generate robust biological answers with, perhaps, more face validity than usual.

Finally, what do journal editors know about a good paper? The Kaleidoscope team have asked ourselves that on many an occasion as our genius went unrecognised, once again, and our manuscript

quickly returned with a polite non-acceptance 'we wish you all the best with your future endeavours'. We speak not, of course, of the *BJPsych*, where editorial quality is without blemish, but those other journals you might occasionally read. Anyway, Schroter et al, who work at the *BMJ*, note⁷ the efforts of a previous editor of *JAMA*, George Lundberg, who admitted setting out to deliberately enhance his journal's impact factor through manipulation of the papers that were accepted. They reasoned that if this can be so gamed, then journal editors at the *BMJ*, where the impact factor rose from 5 in the year 2000 to an eye-watering 96 in the year 2021, must have unrivalled soothsayer abilities in recognising the best of the best research. Testing this, they got ten *BMJ* handling editors to rate over 500 submitted manuscripts with favourable reviews on their estimated citation potential in the year of publication and the subsequent year combined. The selected editors were described as 'fiercely competitive', and, perhaps ever so slightly tongue-in-cheek, it was noted 'We excluded the paid statistical advisors attending meetings in case they were better than us'. The editors were offered one of four predictive categories for each paper: no citations, below average (defined as <10: this is the *BMJ* we're talking about), average (10–17), or high (>17 citations). The median number of citations in the defined period was 9, and the editors' predictions were generally in line with outcomes, though with an awful lot of variability, and over half the time they got the category wrong. They more often underestimated those that would actually go on to get a high citation count than the other way around. Pooling the editors' data together did little to enhance the forecasts, and the authors bravely conclude that 'there is no wisdom of the crowd when it comes to *BMJ* editors'. Perhaps more sanguinely, they add that inferentially, editors are inherently and appropriately cautious and focus more on the quality of a manuscript than any 'superstar' element it might have. Overall, we admire their honesty, candour and publication of their own data: we haven't got around to checking at the *BJPsych*... at least not yet.

References

- Stein SR, Ramelli SC, Grazioli A, Chung JY, Singh M, Yinda CK, et al. SARS-CoV-2 infection and persistence in the human body and brain at autopsy. *Nature* 2022; **612**(7941): 758–63.
- Dohnalova L, Lundgren P, Carty JRE, Goldstein N, Wenski SL, Nanudorn P, et al. A microbiome-dependent gut-brain pathway regulates motivation for exercise. *Nature* 2022; **612**(7941): 739–47.
- Sutton Hickey AK, Duane SC, Mickelsen LE, Karolczak EO, Shamma AM, Skillings A, et al. AgRP neurons coordinate the mitigation of activity-based anorexia. *Mol Psychiatry* [Epub ahead of print] 28 Dec 2022. Available from: <https://doi.org/10.1038/s41380-022-01932-w>.
- Brucato G, Appelbaum PS, Hesson H, Shea EA, Dishy G, Lee K, et al. Psychotic symptoms in mass shootings v. mass murders not involving firearms: findings from the Columbia mass murder database. *Psychol Med* [Epub ahead of print] 17 Feb 2021. Available from: <https://doi.org/10.1017/S0033291721000076>.
- Pitman A, Marston L, Lewis G, Semlyen J, McManus S, King M. The mental health of lesbian, gay, and bisexual adults compared with heterosexual adults: results of two nationally representative English household probability samples. *Psychol Med* [Epub ahead of print] 17 Feb 2021. Available from: <https://doi.org/10.1017/S0033291721000052>.
- Kyzar EJ, Denfield GH. Taking subjectivity seriously: towards a unification of phenomenology, psychiatry, and neuroscience. *Mol Psychiatry* 2023; **28**(1): 10–6.
- Schroter S, Weber WEJ, Loder E, Wilkinson J, Kirkham JJ. Evaluation of editors' abilities to predict the citation potential of research manuscripts submitted to the *BMJ*: a cohort study. *BMJ* 2022; **379**: e073880.