BJPsych | The British Journal of Psychiatry (2018) 212, 189–190. doi: 10.1192/bjp.2018.20

Kaleidoscope

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

Nurture and nature, nurture and nature, go together like a horse and carriage, as the song didn't go. We recognise both genes and environment play a role in mental illness, yet debating the relative role of each must be one of our most common battlegrounds. Twin studies can help delineate genetic contributions, but they do not convey cross-generational transmission, and they inevitably have relatively small participant numbers. Kendler *et al*[1] present another impressive paper on the risk of developing a major depressive disorder mining the Swedish population register, looking at parents and their offspring. Over two million individuals' data were included, clustered to five family 'types': intact, adoptive, not-lived-with father, stepfather, triparental. Triparental was the description given to a family model intersecting the former ones: offspring living with a biological mother from ages 0 to 15, never living with their biological father and spending at least 10 of those first 15 years living with a stepfather. These combinations allowed unpicking of genes and rearing, genes-only and rearing-only associations for major depressive disorder. The correlations were, respectively (drum-roll): 0.17, 0.08 and 0.08. In other words, genes and rearing together had the strongest association with an additive effect, and the judges called it a score-draw for either in isolation. In some senses this is perhaps what we might have predicted, but it is always good to get the data. Perhaps why we fight about these relative inputs is the sociologically interesting question.

Something old: antipsychotic medications work, but what about long-term data beyond the standard 8-week acute phase trials? Hospital admission rates might serve as a proxy marker for longer-term outcomes, and more registry data from those foresighted Scandinavians, this time from Finland. Taipale and colleagues[2] evaluated data prospectively collected from over 60 000 patients with schizophrenia. Median follow-up time was just over 14 years, and almost 60% had a readmission to hospital. Clozapine and long-acting injectables (LAIs), notably olanzapine LAI, were associated with the lowest risk of all-cause hospital admissions. These strong data, from real-world representative samples are starkly juxtaposed against a body of other work showing the significant delay in instigating clozapine – despite guideline recommendations – and the unpopularity of LAI use by many clinicians. It is noteworthy that research exploring patient attitudes often finds them less resistant to LAIs than one might imagine, especially when effort and care are put into education, discussion and joint working. The paper is a call to audit practice: we suspect your managers may have discussed 'bed occupancy' and 'finances' with you in recent times, and there's that old chestnut of 'patient experience' if those drivers don't float your clinical boat.

Something new: organoids – you heard it here first. Psychiatry, we are frequently told, is lost to biological reductionism – we spend too much of our time focusing on isolating biological substrates with methods that use blunt snapshots of people diagnosed with clinical conditions. Until recently, the complex developmental aspects of disorders were, in part, lost because it's unethical to experiment *in vivo* on developing humans. Rather obviously, you cannot take a neonate and deliberately alter their brain (no matter how strong your hypothesis: ethics' committees are funny like that). Enter 'organoids' – awarded 'method of the year' by *Nature Methods*. These *in vitro* miniature brains are derived from induced pluripotent stem cells (iPSC). Mertens *et al* first used the iPSC technique to produce differentiated hippocampal dentate gyrus cells from people with bipolar affective disorder in 2015.[3] They compared the cells derived from people with bipolar affective disorder who were clinically responsive or non-responsive to lithium, and showed the iPSC-derived neurons from both groups showed hyperexcitability. Further, when the cells were treated with lithium, this hyperexcitability disappeared only in the cells derived from people who are lithium-responsive.

Brain 'organoids' have utility because they can be derived from people with clinical conditions, but are 'reset' to their early developmental stage (hence their similarity to stem cells). This facilitates *in vitro* experiments where different physical and temporal features of the developmental trajectory (for example modifying chemical signalling) can be tested experimentally. However, there are limitations: currently, most of the work focuses on specific cell types and intracellular pathologies, and the organoids produced do not have the architecture of tissues. So, for example, it's not yet possible to study networks of neurons synapsing with each other in forming or pruning networks (arguably, one of the key processes underpinning psychiatric disorders emerging during or just after adolescence). Arlotta[4] highlights how microglia (central to pruning processes) are difficult to engineer into organoids because they are derived from the yolk sac and seed the brain mesenchyme in a relatively short period during embryogenesis, where they remain throughout life. Given the vast polygenic complexity of psychiatric disorders, this proposes that iPSC-derived organoids hold significant utility because the resulting cells contained the genome of the person from whom they were sampled. Micro-insults in the cells' development can then be experimentally studied retaining the genotype of the person.

Something borrowed: stimulant medication for mania. Hegerl *et al*[5] randomised individuals with acute mania to receive either methylphenidate or placebo. The backdrop is the 'vigilance regulation model' that proposes that unstable regulation of vigilance with disrupted wakefulness is aetiological for both attention-deficit hyperactivity disorder (ADHD) and mania; this results in homeostatic responses of hyperactivity and sensation-seeking to autoregulate through a stimulating environment. Following on from this, akin to effects in ADHD, stimulant medication would therein putatively help re-regulate this, and be of therapeutic benefit in bipolar affective disorder. Forty-two patients were randomised before the trial was terminated because of an interim futility analysis, the active compound showing no benefit over placebo at 2.5 days. The authors note their relatively small sample size, short trial duration and a medication dose below that typically used in adult ADHD.

On to a different randomised controlled trial but a similar outcome; adolescent antisocial behaviour leads to an approximately tenfold increment in public-sector costs by the time such individuals reach their late twenties. Multisystemic therapy has shown some early promise in reducing this, predicated on family- and home-based treatment that incorporates tailored elements of cognitive, behavioural, strategic and structural family therapies. Fonagy *et al*[6] report on a large pragmatic randomised controlled trial that randomised families with an adolescent member with moderate-to-severe antisocial behaviour to either 3–5 months of multisystemic therapy or treatment as usual. The active intervention was intensive, with therapists meeting the family three times a week over the 3–5 month period, and contact was available 24 hours a day, 7 days a week. An impressive 684 families were included, but at the 18-month intervention end-point, the active intervention showed no benefit in terms of the primary outcome of out-of-home placements, and there were no long-term benefits in behaviour, mental health, social care or educational attainment. Indeed,

https://doi.org/10.1192/bjp.2018.20 Published online by Cambridge University Press

treatment as usual was superior at reducing offending behaviour. Negative trial data can be both a disappointment to research teams and a challenge to get accepted for publication. However, they are vital in progressing our knowledge, and these two recent examples help us by showing what does not work and this may be most important in our current financially restricted times.

Something blue: half of all academic articles are uncited 5 years after publication. That, at least, is the oft-recanted figure from an almost 30-year-old paper in *Science*. An editorial in *Nature*[7] finds that this was probably apocryphal even at the time, although changes to the publishing process, including total academic output and bibliographic software mean it has certainly reduced since, with less than 10% on Web of Science currently remaining uncited (even this is probably an overestimate as it doesn't capture all databases and typos that hinder accurate indexing). Removing self-citations increases the number never cited by half. There is the pleasing story of the Nobel laureate Oliver Smithies who would tell of an early paper of his from 1953 that was never cited, but from which he believed he developed his skills as a scientist. It reminds us of the core values of science in the era of the Research Excellence Framework. Writing in the *BMJ* Jeffrey Aronson[8] asks if authors are to blame through errors in the indexing of their name. As well as problems with hyphenated names, post-nominals sometimes get mistakenly included, leading to a raft of publications ascribed to the hip yet mysterious sounding 'Phil D'. Aronson notes that 'Et Al' is one of our most prolific colleagues, credited with over 50 000 articles on PubMed, and, the piece records, typically as the work's senior author. Perhaps it's all in the paper's title and having something unique to catch a reader's attention. Professor of health law and science policy Timothy Caulfield bemoaned that a quasi-scientific search of 2017 publications found 'Lost in Translation' used in over 36 000 titles that year, 'the Good, the Bad, and the X' in 5600, and 'Mind the Gap' almost 4000 times. At Kaleidoscope we avoid frivolity and jingly subheadings.

Finally, a silver sixpence in her shoe: money doesn't bring happiness – right? Horace pronounced 'As riches grow, care follows and a thirst for more and more'. Well income is associated with happiness, but the relationship is eternally debated. Jebb *et al*[9] explore data from over 1.7 million people in a Gallup World Poll encompassing 164 nations, looking for 'income satiation' – the point when greater income no longer leads to greater well-being. Globally, the figure is an annual household income of \$60 000–75 000 for maximum emotional well-being and \$95 000 for life evaluation: that latter figure is about £70 000 if you wish to compare your wage slip with your mental state and test the theory. There was variation between and within countries – wealthier and better educated nations and individuals being greedier – and for some, in accord with the *Odes*, earning beyond this was linked with reduced life evaluations. Against the authors' hypothesis, there were no differences between men and women in how much money each gender needed for happiness: we are curious how you envisage the direction in which they had predicted the genders would differ. As for us, we primarily take our counsel from the Beatles, so we don't care too much for money…

References

1 Kendler KS, Ohlsson H, Sundquist K, Sundquist J. Sources of parent-offspring resemblance for major depression in a national Swedish extended adoption study. *JAMA Psychiatry* 2017; Dec 13 (doi:10.1001/jamapsychiatry.2017.3828).

2 Taipale H, Mehtälä J, Tanskanen A, Tiihonen J. Comparative effectiveness of antipsychotic drugs for rehospitalization in schizophrenia—a nationwide study with 20-year follow-up. *Schizophr Bull* 2017; Dec 20 (doi:10.1093/schbul/sbx176).

3 Mertens J, Wang QW, Kim Y, Yu DX, Pham S, Yang B, et al. Differential responses to lithium in hyperexcitable neurons from patients with bipolar disorder. *Nature* 20015; **527**: 95–9.

4 Arlotta P. Organoids required! A new path to understanding human brain development and disease. *Nat Methods* 2018; **15**: 27–9.

5 Hegerl U, Mergl R, Sander C, Dietzel J, Bitter I, Demyttenaere K, et al. A multi-centre, randomised, double-blind, placebo-controlled clinical trial of methylphenidate in the initial treatment of acute mania (MEMAP study). *Eur Neuropsychopharmacol* 2018; **28**: 185–94.

6 Fonagy P, Butler D, Scott S, Scott S, Pilling S, Eisler I, et al. Multisystemic therapy versus management as usual in the treatment of adolescent antisocial behaviour (START): a pragmatic, randomised controlled, superiority trial. *Lancet Psychiatry* 2018; Jan 4 (http://dx.doi.org/10.1016/S2215-0366(18)30001-4).

7 VanNoorden R. The science that's never been cited. *Nature* 2017; **552**: 162–4.

8 Aronson JK. Non-existent authors. *BMJ* 2017; **359**: j5706.

9 Jebb AT, Tay L, Diener E, Oishi S. Happiness, income satiation and turning points around the world. *Nat Hum Behav* 2018; **2**: 33–8.

https://doi.org/10.1192/bjp.2018.20 Published online by Cambridge University Press