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Kaleidoscope

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

Why are diagnostic systems so doubted? Recent news of five subtypes of type 2 diabetes was heralded as a personalised medicine breakthrough; curiously, analogous findings in psychiatry are sometimes used to accuse it of being a pseudoscience. It seems a peculiarity that any diagnostic chink in mental health is taken by some as proof of non-existence of a condition, yet those in physical health are seen as eternal shibboleths (no one seems bothered whether 'hypertension', with its expert panel-determined cut-offs, is an 'illness'). In any case, how can we better subcategorise to aid understanding of aetiology and target treatments? Peterson *et al*[1] report on genome-wide association data from almost 10 000 Han Chinese women with recurrent major depressive disorder (MDD); by stratifying participants by exposure to adversity, three new loci were identified that were only associated with MDD in those with *no* history of significant adversity. The findings have a couple of curiosities: first, most gene–environment work has elaborated upon genes that increase risk of MDD when exposed to stress, whereas these findings show loci with maximal impact in those without this; second, they re-raise the old and perhaps unfashionable notions of endogenous and reactive depressions.

Moving to the psychoses, and another large Chinese genetics study; Yu *et al*[2] report on five novel loci in individuals with schizophrenia that were associated with response to antipsychotic medication. A 'discovery cohort' of almost 2500 individuals were randomly assigned to receive one of the six medications: olanzapine, risperidone, quetiapine, aripiprazole, ziprasidone, or haloperidol or perphenazine. Single-nucleotide polymorphisms (SNPs) were evaluated for associations with clinical change over the 6-week study period. Crucially, linkage disequilibrium-independent SNPs that demonstrated potential associations were then prospectively tested in a 'validation cohort' of over 1300, which confirmed the finding. Both general medication responses and – for olanzapine, risperidone, and aripiprazole – drug-specific loci were determined. The loci are regions containing genes involved in synaptic function and neurotransmitter receptors. Current utility may be hindered by small effect sizes from individual SNPs, but personalised medicine and refined diagnostic categories are coming to psychiatry: slower than we'd like, but whatever the nay-sayers say…

Why are robust study methodologies so challenged? Meta-analyses – the bedrock of evidence synthesis – have come under fire recently, an exemplar being the attacks on the rigorous work by Cipriani *et al*[3] supporting antidepressant efficacy. Data science has advanced owing to computational resources that enable analyses using algorithms which were hitherto intractable – you couldn't really do network meta-analysis on an old 1985 Intel 80386 desktop personal computer, but today you can run huge analyses on your laptop. For a real-world anchor, 10 years after its introduction, the 80386 became the CPU for Nokia's 1996 'Communicator' mobile phone. However, just because you can collate, merge or fuse, and then analyse huge swathes of data, doesn't mean you should. Gurevitch *et al*[4] review the history and current state-of-the-art of meta-analytic methods. Their theoretical origins date to the early 1900s: in 1977, the method for standardising outcome measures was published (and used for a meta-analysis of the efficacy of psychotherapy); and then in 1985, the first dedicated meta-analysis textbook was released. Their exponential growth really took off around 1995 (but is unlikely to have anything to do with the Nokia Communicator), some 2 years after the establishment of the Cochrane Collaboration.

Gurevitch *et al* tackle the 'apples and oranges' argument – how can a bunch of studies ever be meaningfully combined? They draw a distinction between summarising a small number of studies in homogeneous populations, and the broader goal of arriving at a consensus (for example, for treatments) across larger numbers of studies and more heterogeneous populations. They argue that only meta-analyses using well-established statistical methods (appropriate effect size standardisation, weighting – e.g. by inverse variance – and heterogeneity analyses) should be considered robust. One interesting development is that researchers' expectation of meta-analysis has led individual studies to adopt compatible reporting standards. Another polemic is credit assignment – meta-analyses attract high citations, but the primary sources included in a meta-analysis do not. So, one could argue, if your paper gets included in a published meta-analysis, you can expect to see your citation count drop as more people cite the meta-analysis than your paper. No contemporary paper on any topic in science would be complete unless it mentions artificial intelligence. Here, the authors suggest that (you guessed it) artificial intelligence can help in automated screening of papers and sources for inclusion in meta-analyses and (again, you probably guessed it) they call for 'greater trans-disciplinary' collaboration from statistics, computer science, biology, social science and … well, 'other scientific fields'.

Why do politicians disbelieve or forgo science when setting drug and alcohol policy? Or is it perhaps pontificating scientists avoiding 'real world' complexity who miss the point, or clinicians who cannot see the necessary social trade-offs in complex legislative processes? Indeed, what is 'good' drug policy? Cultures and jurisdictions vary, from total prohibition to free market economies, with most somewhere in the middle. Certainly, just telling people not to consume alcohol or drugs seems to have run aground on the shores of hopeless optimism, blown by the winds of human curiosity. Evoking his seminal work on drug harms, an impressive team lead by David Nutt[5] puts forth a novel multi-criterion decision analysis approach for formulating and appraising drug policy, focusing on alcohol and cannabis. They cluster 21 key criteria into seven areas – health, social, political, public, crime, economic and cost – and model the influence of various legislative frameworks on each of these clusters. Of the four generic regulatory regimes defined, 'state control' was deemed most appropriate by this expert panel for both alcohol and cannabis. Of course, different individuals and stakeholders will prioritise each cluster in a different way, but this, the authors argue, is the strength of their model, allowing a dispassionate deconstruction of the underlying factors involved in legislative approaches and, thereafter, greater ease in reaching consensus results on social and political approaches. Debates on the roles of alcohol and drugs in society are complex and vary between different jurisdictions, cultures and interest groups; the framework offers an attractive way to open up and compare various societal options, where neither the scientist nor politician (nor anyone else) has the dominant narrative.

Why is psychopathy always so fascinating to psychiatrists and the public? Theory of mind (ToM) work has suggested that the disregard for social norms and others' welfare seen in psychopathic individuals – previously pejoratively called 'moral insanity' – is an issue of social-affective processing. Drayton *et al*[6] explored a task that tapped into 'automatic' ToM in a cohort of prisoners: this engaged individuals in *unintentionally* representing the perspectives of others, as well as the more standard controlled tests directly enquiring about this. Fitting with previous work, they showed that psychopathic individuals have intact ToM and *can* understand others' perspectives (controlled ToM testing). However, novelly, they found deficits in

automatic ToM that correlated with psychopathy and real-world antisocial behaviour (measured through assault charges). Their data suggest that the core deficit in psychopathy may be a cognitive one, with a reduced ability to *automatically* think from another's perspective. Perhaps somewhat ominously, psychopaths can understand others if they deliberately choose to consider this, but typically do not do so without a goal-relevant situation for them: if there's nothing in it for them to try to intentionally comprehend you and your thoughts, it doesn't occur to them to do so, and they won't.

Why do doctors bullshit their patients? Not you, of course, but, you know, your colleagues. 'Nudging, informed consent and bullshit' was a paper title always likely to make us read further, and not just because of the missing Oxford comma. Writing in the *Journal of Medical Ethics*, William Simkulet[7] notes how some have argued that when obtaining consent, while not restricting a patient's options, doctors should nevertheless try nudge an individual towards the decision they (the doctor) believe best. We all know that goes against the pure principle of this process, but we suspect you can fully picture the scenario, and wonder how many of you feel able to cast stones at others who might have done this. A core tension in the move away from patriarchal healthcare was that professionals are experts with a moral duty to provide the best advice and care, but while patients typically respect that expertise, they also want the 'whole truth' and can yet make different and unwise capacitous decisions for any number of reasons. 'Nudging' is using one's influence to exploit a non-rational part of a patient, to alter, without forcing, behaviour. Simkulet says that well-intentioned nudging behaviour is incompatible with truth-telling and, rather, fits Harry Frankfurt's definition of bullshit. If we don't provide unambiguous information, then we have not truly received informed consent. One for your next peer-group meeting…

Why is there so much #fakenews about, and does it matter? Using Twitter, Vosoughi *et al*[8] sought to find how verified true and false news stories diffused between 2006 and 2017. They defined a rumour as a single Tweet that makes some claim or assertion and is then Retweeted, and subsequently defined a cascade as an unbroken chain of Retweets originating from that single source. The number of cascades is defined as the number of times the rumour (not the original Tweet) is the source of another chain. They analysed over 126 000 rumour cascades, distributed by some 3 million people over 4.5 million times. Each claim or rumour (for a cascade) was classified as true or false using six separate fact-checking sources possessing high agreement (> 95%), and measures were derived for the number of users, depth (number of new individual users independently Retweeting) and virality. All of these measures increase as a claim or rumour is Retweeted.

Overall, they found that the highest number of false rumour cascades were political in nature, and at 'peaks' corresponding to the most recent US presidential elections (2012 and 2016 – enough said), as well as the annexation of Crimea in 2014. After politics, rumours were most commonly about urban legends, business, terrorism and then science (interestingly, entertainment was second from last, just above natural disasters). In terms of patterns of diffusion, Vosoughi found that truths rarely diffused as much as falsehood: the top 1% of false news cascades routinely reached between 1000 and 100 000 people (but truths rarely made 1000 people). Truths also diffused more slowly – taking six times as long to reach 1500 people and 20 times as long to achieve a depth of 10. In terms of individual behaviours, people were 70% more likely to Retweet false than true news. A confirmatory analysis using three independent (human) reviewers of true and false Tweets – instead of the fact-checking sources – did not affect the results. Interestingly, there have been recent concerns about the behaviour of 'bots' (software imitating a real Twitter user but, usually, behaving with an implicit agenda) influencing the spread of 'fake news' online – these appear unfounded according to Vosoughi's analyses, where removing cascades identified as originating from bots did not change the results.

Finally, why are conspiracy theorists so impervious to contradictory evidence? Ever popular, or at least contemporaneously fascinating, they can engage our own field of psychiatry in peculiar ways, notably proposing that we are heartless reductionist societal manipulators and the henchmen of 'big pharma': that is of course true, but we can't let the public find out. Klein and colleagues delve[9] into the world of online fora, a rich seam of conspiracy theorising; they report on a unique approach to unpicking what can be a nebulous environment, using non-negative matrix factorisation to model posters' contributions in a large forum at Reddit.com that tracks back over several years. Individuals typically clustered to an area (think 9/11 through faked moon landing to Obama's birth certificate), with subpopulations emerging based on their background beliefs and motivations. The authors propose that the simplistic model of so-called 'monological' believers, where a single idea spreads to become an all compassing mindset explaining all current events (think illuminati), is just that – simplistic – and that such individuals account for only a small minority, although they can be a very vocal subgroup. Further, neither pure irrationality nor preoccupations accounted for the diversity observed. The authors state that some conspiratorial thinking is very widespread, and they wryly note academics' discussions on the actions of grant-awarding bodies. They argue that conspiratorial concerns appear to link a rather heterogeneous group of individuals; however, we're not sure we believe them – after all, who funded their work, and why?

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