BJPsych | The British Journal of Psychiatry (2022)
221, 709–710. doi: 10.1192/bjp.2022.137

Kaleidoscope

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

Medication non-serious adverse events (NSAEs) are common yet frequently overlooked in the scientific literature. Chevance et al[1] conducted an international survey of patients and clinicians (available in English, French and German) to identify the most important antidepressant NSAEs. Overall, this included 1631 patients with severe depression (four-fifths of whom were women) and 281 healthcare professionals (HCPs, four-fifths of whom were psychiatrists) from 44 countries. The most important NSAEs for patients, in order of frequency, were deemed to be insomnia, anxiety, fatigue, weight gain, agitation and sexual dysfunction. There was considerable heterogeneity insofar as no NSAE was selected as being in the top three by more than a quarter of participants, with the sole exception of insomnia. Interestingly, neither depression severity nor whether one was taking medication at the time had any impact on rankings. For HCPs, the order was: sexual dysfunction, weight gain, erectile disorders, sleepiness, agitation and nausea. Further clinically important issues included emotional numbing and problems with concentration. Of course, survey data always come with significant caveats, not least via the issue of potential selection bias. Nevertheless, the authors note that discussions with those in real-world clinical settings should occur more often and call for more systematic collection of these 'less severe' but very real and common problems. Research trials need to pay more attention to these important factors.

Hypochondriasis isn't rare, but is often ignored or dismissed by doctors. After all, surely it means there is nothing wrong with you? Well, by definition it clearly does mean that there is an unreasonable preoccupation with the possibility of having an illness or disease and a repeated need for reassurance, but, equally, that is distressing and has a negative impact on quality of life for the individual. Fineberg et al[2] carried out the first meta-analysis of treatments, with some clear implications for future research. Cognitive–behavioural therapy (CBT) and selective serotonin reuptake inhibitors (SSRIs) are the mainstay of treatment. This is perhaps not surprising when one considers that hypochondriasis has been classified as an obsessive–compulsive disorder in ICD-11. Thirteen randomised controlled trials (RCTs) were included, 12 involving CBT (N = 1212 participants) and three using SSRIs (N = 193). Both interventions were found to be effective in the acute treatment of hypochondriasis, with some data that an earlier age of intervention is associated with better outcomes. There was a paucity of data on longer-term outcomes, with a maximum follow-up of 16 weeks. In direct comparison studies, SSRIs showed a numerical but not statistical advantage over CBT. Importantly, the authors determined considerable problems in the literature; funnel plot asymmetry suggested publication bias, and 11 of 13 studies were rated as high for research allegiance bias in favour of CBT, something that significantly inflated effect sizes. In particular, almost half the RCTs used waiting list controls as the comparator to the active psychological intervention. The authors propose a way forward, through a definitive, fairly matched controlled trial, with intention-to-treat analysis and strategies to ensure treatment fidelity. With rates of hypochondriasis of up to 4% of the general population, 8% of those attending general practitioner surgeries, and 12–20% of those attending specialist clinics, we concur with the authors about this need and with their comment that this is a cohort too frequently overlooked.

Our brains make us unique as a species, but which evolutionary factors drove their special development? Clearly, brains don't fossilise well, and the minds of our ancestors are inaccessible, but some recent comparative genetic studies are revealing our phylogenetic past. Kaczanowska et al[3] reconstructed human cognitive evolution via comparative mammalian neuroanatomical and genetic data to determine selection of task-related functional networks. Shared and divergent changes between animals and an understanding of when in the ancient past they separated can help us to map phylogenies, even when species are extinct. In particular, for ancestral human species, these can be extrapolated by exploring selection pressures on the human brain. Adaptive evolution was found to have shifted in our very ancient hominoid ancestry – some 26–19 million years ago (mya) – to more recent hominids (19.7–7.4 mya) via a change away from motor control functional networks towards those involved in attentional processing. As we evolved from hominids to hominins (our more recent lineal forebears, 7.4–1.7 mya), selection in functional networks for language appears, with adaptive evolution for strategic thinking seeming to appear in the past 800 000 years. This methodology is a clever way to side-step the challenge of interpreting behaviour from fossil 'bones and stones' and gives an inferential framework and timescale of when various human cognitive adaptations began to more strongly emerge.

To a potentially more contentious question: what, if anything, delineated us cognitively from our sister species *Homo neanderthal*? Neanderthal successfully roamed Europe for hundreds of thousands of years as we sapiens were co-evolving in our African homeland. Our last shared common ancestor remains debated, as do the various cultural and cognitive differences between us. Neanderthal has certainly undergone a mini-renaissance from the erstwhile stereotype of the brutish caveman, but while differences between our species reduce, there remains inference of their more limited meta-cognitive abilities as manifested through their general lack of symbolic art, ritualistic grave goods and less technologically sophisticated tools. The total cranial volumes of neocortices of the two species are similar (if anything, that of Neanderthal is perhaps a bit bigger), so it's clearly more than a consequence of crude brain size. Pinson et al[4] tackle this by comparing genomes – the Neanderthal one remarkably having been available from extractions from fossilised tissue for over a decade now – and paying particular attention to genes involved in embryonic neurogenesis. A critical difference discovered was an amino acid substitution in the *TKTL1* gene of modern humans that encodes a key enzyme in the metabolic pathway of acetyl-CoA creation. What difference does this single change make? Looking at rodent and human brains, as well as human cerebral organoid cultures, the authors determined that the sapiens version, *hTKTL1*, promotes proliferative abundance and a self-amplifying expansion of progenitor basal radial glial cells in mouse embryos; the neanderthal version, *aTKTL1*, just did not do this. A single amino-acid-based change, from lysine to arginine, absent in Neanderthals but particularly prevalent in sapiens fetuses, appears to have produced a very significant brain change of greater numbers of neurons produced within developing prefrontal lobes. The behavioural impact of that seems likely to be debated in anthropology circles for some time to come.[1]

Algorithms, like people, are arguably most interesting when they go wrong. In applications of machine learning, showing algorithms examples designed to break their predictive abilities is an established method of understanding how and what is being inferred from the training data. A new paper in *Nature* by Greene et al[5] attempts to leverage a similar idea in understanding the generalisability of brain phenotypes – that is, where neuroimaging is used to establish

[1] If the topic interests you, the College textbook on evolutionary psychiatry, edited by Abed and StJohn-Smith has just been published by Cambridge University Press.

a relationship with some behavioural, cognitive or clinical entity: for example, functional connectivity in a brain region being able to discriminate between disorders. Developing these models is a high-stakes affair; if one succeeds in developing a model that generalises (i.e. the model can be shown to perform well on new data it was not trained on), then you can wave a flag declaring you have a test for that disorder with some positive predictive value. A key question is what to do for cases (people) on which the model declares the wrong phenotype (misclassification). To progress this, we need to understand for whom and why the models fail. Using neurocognitive testing as the phenotype(s) of interest, Greene et al used data from three different data-sets to train classification algorithms to use functional connectivity features to discriminate between phenotypes. They used a variety of validation and model selection regimes to ensure the algorithms were performant and able to generalise and were not overfitting the training data-sets. They then identified which samples from each of three data-sets were correctly classified participants (CCP) and which were misclassified participants (MCP). In doing so, they could establish that CCPs were – on the whole – correctly classified in their 'home' classifier as well as in classifiers trained on the other two, independent data-sets. The MCPs were also consistently misclassified across the different classifiers. This suggests that all classifiers were learning some consistent stereotyped functional connectivity profile for each of the phenotypes. Importantly, the MCPs appeared to belong to the same, or very similar, phenotypes, and the profiles of the other features (covariates) – such as demographics that aren't themselves functional connectivity features – were also similar in the MCPs.

So, the algorithms are learning prototype functional connectivity patterns that are associated with phenotypes (cognitive domain performance) but are 'tricked' (misclassifying) on some people who don't fit that stereotypical pattern – and those people have similar covariate profiles (clinical and sociodemographic). The authors give the concrete demographic example of level of education and neurocognitive testing score (the phenotype): the stereotype learned by the classifiers was 'higher educational attainment, higher neurocognitive performance'. Those participants who break that stereotype (those with lower educational attainment but higher neurocognitive performance and the complementary set of people with high educational attainment but poor neurocognitive performance) were misclassified. The authors repeated their analyses using four different supervised learning algorithms (support vector machines, a regression-based method, bagging ensembles of weak learners and a neural network) to ensure that their results weren't algorithm-specific. Of particular note, in two of the data-sets, some participants were being treated for psychiatric conditions. For those people, medication use and symptom severity were correlated with a lower probability of being correctly classified (the implication being that mental illness is relevant to the stereotypical patterns learned or inferred in brain-phenotyping work, at least in so far as neurocognitive phenotypes are concerned). The paper shows the problem of one-size-fits-all modelling but, moreover, provides a framework to redress this to allow neural circuits underlying specific phenotypes to be elucidated.

Finally, 'To live is to suffer, to survive is to find some meaning in the suffering' taught Nietzsche. The term mental pain is immediately recognisable and the foundation of much art. However, although ubiquitous, internal anguish is both totally known and without an agreed-upon definition, and it is rarely formally evaluated despite being a known risk factor for suicide. A recent systematic review in *Evidence-Based Mental Health* set out to explore the concept.[6] It pulled together all known measures of mental pain – their definitions, scales, development and psychometric properties – to look for similarities and core features. Gathering any scale from peer-reviewed published studies (1999–2021) whose purpose was to measure 'mental pain', 'psychological pain', 'psychic pain', or 'psychache', ten were identified. The first layer of analysis was semantic, identifying all words used to indicate pain and its location. From there, qualitative content analysis coded the broader domains covered to create a visual map calculating their similarity. They were found to be wildly different, with no consensus in terms of verbiage, theoretical foundation, definitions of mental pain or broad domains. This was echoed by the Jaccard similarity scores: the highest level of similarity for a single measure to all others was 'weak', with four instances of measures scoring zero similarity. COSMIN (consensus-based standards for the selection of health measurement instruments) was used to evaluate the measures themselves. This hierarchical approach orders evaluation with an automatic stopping point if a previous level is deemed inadequate. Development was assessed first, as the foundation from which all aspects of a scale emerge, by looking at both scale design and asking patients about the measure. Content validity investigated the items' relevance and context of use, comprehensiveness and comprehensibility. Finally, as long as the previous two areas of investigation were rated above inadequate, psychometric properties would be evaluated. The lack of information provided about each scale's development prevented any real evaluation of this parameter. Similarly, content validity failed to find a single study with healthcare professionals and patients evaluating the measure on the key aspects. As such, all measures were deemed inadequate, and subsequent investigation into the psychometric properties was halted. The authors note that, currently, no measure can be recommended for use over any other because of the glaring lack of information required to evaluate them. They also make particular mention of the lack of patient involvement in the assessment of tools designed for people to self-rate their mental pain. Although these measures can certainly be considered important for providing a foundation for our efforts to conceptualise mental pain, their shortcomings necessitate that we develop something to fill these gaps. Clinical practice, research and people will benefit from a systematic clarification and unification of the concept and total transparency in the development of future measures. Whereas science fails in its grappling with the concept, we're delighted to note that poets since antiquity have profoundly understood mental pain. We'll leave the last words to Gerard Manley Hopkins: 'O the mind, mind has mountains; cliffs of fall/Frightful, sheer, no-man-fathomed'.

References

1 Chevance A, Tomlinson A, Ravaud P, Touboul S, Henshall C, Tran V-T, et al. Important adverse events to be evaluated in antidepressant trials and meta-analyses in depression: a large international preference study including patients and healthcare professionals. *Evid Based Ment Health* [Epub ahead of print] 29 Jul 2022. Available from: https://doi.org.10.1136/ebmental-2021-300418.

2 Fineberg NA, Pellegrini L, Clarke A, Perera U, Drummond LM, Albert U, et al. Meta-analysis of cognitive behaviour therapy and selective serotonin reuptake inhibitors for the treatment of hypochondriasis: Implications for trial design. *Compr Psychiatry* 2022; **118**: 152334 (2022).

3 Kaczanowska J, Ganglberger F, Chernomor O, Kargl D, Galik B, Hess A, et al. Molecular archaeology of human cognitive traits. *Cell Rep* 2022l **40**: 111287.

4 Pinson A, Xing L, Namba T, Kalebic N, Peters J, Oegema CE, et al. Human TKTL1 implies greater neurogenesis in frontal neocortex of modern humans than Neanderthals. *Science* 2022; **377**, eabl6422.

5 Greene AS, Shen X, Noble S, Horien C, Hahn CA, Arora J, et al. Brain-phenotype models fail for individuals who defy sample stereotypes. *Nature* 2022; **609**, 109–118.

6 Charvet C, Boutron I, Morvan Y, Le Berre C, Touboul S, Gaillard R, et al. How to measure mental pain: a systematic review assessing measures of mental pain. *Evid Based Ment Health* [Epub ahead of print] 28 Jul 2022. Available from: https://doi.org/10.1136/ebmental-2021-300350.

https://doi.org/10.1192/bjp.2022.137 Published online by Cambridge University Press