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CrossMark

Kaleidoscope

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There has been a welcome growth in cross-disciplinary research integrating social, cultural and community engagement (SCCE) to positively have an impact on mental health. The advantages are both gains in enhancing well-being and improving mental health, and also potentially preventing the occurrence of mental illness in the first place. Community 'assets' can vary from active engagement such as participating in sports, community and voluntary groups, to more passive enjoyment of museums, nature and the local environment, and heritage sites. It is clear these are not 'run' by health and social care services, although there is an increased prominence in 'social prescribing'. However, some observers have questioned if the field is necessarily focused upon the issues of greatest contemporary relevance and importance (or indeed if it is established what these are).

In an attempt to clarify the focus of SCCE, Fancourt et al engaged over a thousand key stakeholders in a six-phase design that aimed to integrate findings for a collective prioritisation of critical questions for SCCE research.[1] Four major themes emerged: the mode, process, impact of engagement and infrastructure required to facilitate this. There is a need to better focus on intervention effectiveness and cost-effectiveness, and elucidation of the theory and mechanisms behind these. Breaking down barriers to collaboration, and ensuring sustainability are also considered key. The authors argue that this moves SCCE work from being a subset of other areas, to its own overarching topic with key research priorities. They note how there are an estimated million 'assets' in the UK, including over 40 000 choirs, 1300 theatres, 150 000 sports clubs and 300 000 voluntary associations and community groups. Something for everyone, we would think and a re-emphasis of the broader social determinants of health and well-being. They also highlight that the findings are particularly timely as we – hopefully – approach the end of the pandemic, yet – challengingly – will likely face enduring mental ill health sequelae for which wider non-medical interventions and activities will be crucial.

The end of a calendar year inevitably brings about cultural rankings of the best stuff in the past year, decade or century. And of course, they are mostly wrong (Abbey Road is not all that great, and Annie Hall is far from being the funniest film ever*). What were the most important statistical ideas in the past 50 years? Gelman & Vehtari present their opinions of these, starting from bootstrapping.[2] Say you want to estimate the average height of a population but can only afford to obtain a sample of $n = 100$ random observations from the population and you have no idea about the underlying distribution of the population – so for example, you cannot assume a symmetric, normal, or 'bell-shaped' distribution. A summary statistic of the 100 observations might be the mean but this might not be reliable because the population distribution is not actually symmetric. With bootstrap resampling, we assume that our original $n = 100$ sample is representative of the population (whatever that might be) and put these 100 observations in a hypothetical bag. We randomly pick one observation from the bag, make a 'copy' for a new 'fake' sample and (this is important) replace the observation *back* in the bag. Repeating this 100 times, we have a new 'fake' population sample and we compute our summary statistic for this fake sample. Do this 1000 times, and then we can form a histogram of the 1000 fake sample means – if this histogram is narrow we have some reassurance that the mean is a useful representation for the underlying population of people's heights. The same idea can be applied to inferential statistics (such as hypothesis tests) when we have small samples or cannot make assumptions about theoretical population distributions.

Another 50-year highlight from Gelman & Vehtari is *overparameterised models* and *regularisation*; that is, how can we fit models with vast numbers of parameters often *exceeding* the number of samples/observations while at the same time avoiding overfitting? This is the problem where a complex model exhibits so much flexibility it will fit anything, including random fluctuation or noise in the data, simultaneously failing to capture the underlying trend or pattern in the data. Regularisation methods offer to help in this situation and reduce overfitting by placing constraints on the model parameters or output of the model. This idea is vital in biosciences and medicine because of its applications in massive biological datasets, like neuroimaging and genomics where we generally have few samples (tens or hundreds) but a model requires thousands of parameters. And of course, current machine-learning techniques would not be possible at all without regularisation methods where a typical model has of the order millions of parameters and thousands (or tens of thousands) of observations.

One unifying theme in Gelman & Vehtari's survey (also including Bayesian and robust inference, counterfactual causal inference, multilevel models, generic model estimation algorithms and decision analysis) is *computation* both as a tool (for example for data visualisation, crunching numbers quickly and accurately) and as an *enabler* – for example bootstrap procedures are wholly impractical without computers. Further, computer-enabled statistics has meant that almost anyone with a laptop can start analysing data and data-sets too large for any one person or machine to analyse ('big data') and these can now be processed and visualised *en masse*.

Oftentimes elucidation of biological processes can feel a world away from the deep pain and suffering we see in human experience. Voices calling for us to bridge the lab and the clinic for a better gestalt approach to treatment are growing ever louder, but are often considered to be peddling a 'nice to have' rather than an essential to delivering quality care. An exciting, and controversial, older example of this potential bridge is the discussion of medications such as propranolol being used to disrupt memory consolidation after traumatic events. By understanding the way in which memories form, a precise interruption of the process could potentially prevent the anguish and disability that can come from resulting phobias or post-traumatic stress disorder. Although with memory being so central to our identities, growth and responsibility, not to mention the potential for abuse, this still sits firmly with bioethicists. However, a recent paper in *Neuropsychopharmacology* brings a new, perhaps less controversial, version of this idea from the world of stress.[3] Within animal models, acute and chronic stress cause changes in dendritic architecture within the basolateral amygdala (BLA), unique from that seen in the hippocampus, which corresponds with an increase of anxiety-like behaviour after a delay of 10 days.

The authors explored the oral administration of corticosterone 24 h after a 2 h immobilisation stressor in rats on amygdalar dendritic plasticity and animal models of anxiety behaviour. Animals within the control group experienced an increase of endogenous corticosterone signalling, followed by a delayed reduction of exploratory behaviour in the elevated plus maze, reduced social

* These provocative musings of the second author in Kaleidoscope are clearly frankly wrong, and designed primarily to upset the sensibilities of the lead author. However, as the lead author controls the copy that goes to the journal, he herein highlights this egregious cultural error, and furthermore points out the limited musical talent of Tom Waits.

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interaction and an increase in BLA spine density 10 days later. In the treatment group, corticosterone administration appears to have supplanted the natural surge of stress hormones and prevented the development of detrimental impact seen at the cellular and behaviour levels. Although not without its own philosophical questions, the use of acute trauma, and oral administration of treatment 24 h post-event, provides a clinically relevant model showing the exciting potential to reverse the delayed impact of traumatic stress by harnessing the somewhat counterintuitive protective effects of glucocorticoids.

Which evolutionary changes underpin the unprecedented growth of human brains in our ancestral lineage? Any adaptive changes growing that calorie-hungry organ could only be supported once ancient hominins had ready access to surplus energy – the cooking of food appearing key – but what were those changes? Two processes are possible: alteration of protein sequences – 'making new things' with DNA; and differential gene expression – changing the regulation of how existing proteins are expressed. There is actually relatively little evidence for either. Regarding the former, if one explores differences in intelligence between us and other great apes, it does not seem as though we can link this to different neural proteins compared with those of our hominid cousins. So attention turns to the latter, that we primarily express them differently. Liu & Robinson-Rechavl[4] describe a new method for the historically difficult process of determining positive selection on transcription factor binding sites – in other words the regulation of expression – that did not require the detection of accelerated evolution or *a priori* definition of nearby non-coding neutral sites. They used this to compare positive selection at the binding site of CTCF, a highly conserved transcriptional regulator, between human and mouse cell types. Human cells related to brain function (but not other human cell types) had the highest proportion of positive selection, occurring on a genetic lineage that has occurred since divergence from chimpanzees. The findings support the long-proposed, but until now less evidenced, hypothesis that it is adaptive regulation and accelerated gene expression that underpin our species unique brain growth.

N-acetylaspartylglutamate (NAAG) is a ubiquitous, but hitherto unglamorous and understudied neurotransmitter that is co-released with glutamate. It is a selective agonist for the metabotropic glutamatergic receptor mGluR3 found on astrocytes that facilitates glutamate re-uptake. Its roles have thus been linked with limiting glutamate excitotoxicity and as part of a negative feedback loop for glutamate signalling. More recent work has linked the mGluR3 with working memory circuitry in the dorsolateral prefrontal cortex (DLPFC) of primates, the DLPFC being one of the key evolutionary areas of brain growth in our own species. Zink et al report on a fascinating, complex investigation of this.[5] They looked at the relationships between the expression of the genes *FOLH1* (coding for GCPII, which regulates the amount of NAAG in the synapse) and *GRM3* (coding for the mGluR3). They found that a missense mutation of *FOLH1* was associated with decreased NAAG, and that NAAG levels in the synapse were positively correlated with cognitive performance. Genetic variants of *FOLH1* are associated with IQ in the general population, and also with cognitive impairment in schizophrenia; these data show how this might occur. NAAG–mGluR signalling appears to have had an important role across evolutionary time in the development of human intelligence in our expanding DLPFC. Practically, this information also offers the possibility of treatment: increasing NAAG via FOLH1/GCPII inhibition putatively might enhance cognitive performance.

Finally, *glycobiology* is your new word this month. Glycosylation is the highly regulated enzymatic modification of proteins through the addition of sugars. These changes have important complex effects for cells and ultimately our whole bodies; might any abnormalities of such essential processes underpin any psychopathology? Mealer et al discuss emerging findings from large-scale genome-wide association studies in psychosis.[6] They note that one of the strongest coding variants in such studies is a missense mutation in the manganese transporter *SLC39A8*, which is linked with altered glycosylation. The finding holds true for variants of several other genes that have been clearly linked with both schizophrenia and encoding glycosylating enzymes. Adding to the link, some critical proteins involved with the dopamine D_2 receptor, glutamate receptors, complement-associated proteins and voltage-gated calcium channels require modification via glycosylation. The roles for glycans in optimising functioning are varied and not yet fully understood, but include cellular localisation and internalisation of receptors, and protein trafficking. The authors summarise that it might be that pathological post-translational glycosylated changes of some key proteins underpins much of the aetiology of psychoses, at least in some cases across this heterogeneous spectrum. There is much work ahead to determine if and when this is the case, and the precise (pathological) mechanisms through which this might occur. However, their hypothesis certainly offers potential downstream therapeutic targets.

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