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Kaleidoscope

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Intimate partner violence (IPV) is underreported and underdocumented, but it is the most common form of violence worldwide and makes a significant contribution to subsequent mental health problems. The *Lancet Psychiatry* Commission on IPV[1] sets out what we know and provides a road map for where we need to get to, particularly in secondary mental healthcare. Variation is notable by country (with national income level a significant factor), along with any minority status, but overall it's estimated that 27% of ever-partnered women will experience physical or sexual IPV in their lifetime, including almost a quarter of those aged 15–19 years. Exposure to IPV and suffering mental illness (particularly substance use) increase rates of perpetrating further violence, but the authors note the ethical and stigmatising complexities of this, including potentially pathologising women's responses to violence and oppression. A key message from the paper is that although IPV is endemic, it is not inevitable, and there are evidenced preventive and interventional opportunities at the level of the individual, the family, the community and society itself.

A primary preventive approach recognises how IPV lies alongside a spectrum of societal oppression of women. Opportunities for positive change include parenting- and schools-based teaching of non-violence norms, enhancing educational, employment and poverty-reducing programmes for women, and targeted substance use resources. Discrimination against women through extant laws and policies such as those surrounding divorce, property ownership and inheritance are rightly called out. Survivors of IPV have been inadequately involved in service development and assessment, although it is acknowledged that these services can be retraumatising to some, especially where care provision has been substandard. Inevitably, beyond capturing some headlines, we cannot do justice to the full report here. We can only commend the full piece to you and concur that reducing IPV will improve mental health outcomes and countless lives. This is everybody's business, and in mental health we need more co-produced gender-sensitive, trauma-informed approaches.

Cellular mechanisms underpinning autism spectrum disorder (ASD) are not well understood, but recent work implicates abnormalities in astrocyte activity. ASD is highly heritable, but no common genetic biomarkers have been discovered; the inference is that there are various pathways to a common pathophysiological end. Accumulating data suggest that synaptic dysfunction may be important as part of the aetiology of ASD, and symptoms often begin at a developmental time of significant neuroplasticity. Astrocytes have crucial roles both in maintaining the extracellular space and in modulating neuronal plasticity through gliotransmissioned alterations to spinal arborisation and pruning, and modulating long-term potentiation that underpins much learning and memory. We forget, perhaps, the scale and intimacy of this relationship, with a single human astrocyte contacting almost two million synapses. Allen et al[2] transplanted mouse-model ASD astrocytes into previously healthy mice, which induced repetitive behaviour and concomitant problems in memory and neuronal long-term potentiation. The transplanted cells were found to show greater calcium fluctuations, and this was associated with lower spine density and accompanying decreases in brain network activity. Exaggerated Ca^{2+} signalling is proposed as the astrocyte-mediated driver of ASD phenotypes, and proteins involved in such calcium regulation have been shown to be differentially expressed in these cells. In mouse ASD models, it has been possible to correct some plasticity signalling deficits, including via full genetic knockout of inositol 1,4,5-trisphosphate receptors. Much further work is required, and the authors note astrocyte heterogeneity and that different sub-populations variously affect neuronal functioning.

Binge drinking during adolescence disrupts a critical period of brain development and confers a higher risk of psychiatric conditions in adulthood, including anxiety and alcohol use disorder (AUD). During this time, a cascade of transcriptional changes, epigenetic modifications and connectivity alterations are occurring. At the centre of these is *Arc*, an immediate early gene and key regulator of synaptic structure associated with cognition, emotion and addiction behaviours. Upstream from *Arc*'s promoter, the synaptic activity response element (SARE) is an enhancer region conserved across species that is negatively affected by adolescent alcohol use. This repressive epigenetic remodelling leads to a lifelong decrease in Arc expression in the amygdala, an area critical for emotion and memory, in both humans and rodents. This type of epigenetic dysregulation has been well documented in several psychiatric disorders and AUDs, although to date the connection between bingeing patterns of alcohol consumption and altered transcription modifications has always been correlational.

A *Science Advances* paper[3] speaks to causation using CRISPR/dCas9 technology. Rats given intermittent alcohol throughout their adolescence, the human equivalent of 10–18 years of age, displayed increased anxiety in behavioural tasks and showed a preference for alcohol consumption in adulthood. These effects were mimicked when they manipulated the histone methylation of the SARE region of *Arc* in the amygdala of adult rats without alcohol exposure, making *Arc* less accessible for activation. Importantly, in adult rats that had underwent the binge alcohol protocol in adolescence, increasing histone acetylation of SARE allowed normal levels of Arc expression in the amygdala and completely reversed anxiety and alcohol preference levels to those of controls. Although many of us may wish for a way to erase the consequences of our youthful choices, beyond burning photos and yearbooks there haven't been many options. Truly understanding the epigenetic regulatory mechanisms that translate adolescent binge drinking into a lifelong propensity for anxiety and AUD may provide a molecular reset button. Though #justinrodents, this epigenetic editing within the amygdala mitigated all behavioural evidence of adult psychopathology usually seen with repeated exposure to high concentrations of alcohol in adolescence. If successfully expanded to humans, it could open the door to treatments and prevention of AUD, for which there are currently few effective interventions, and thus an alleviation of significant individual and public health burdens.

'No person will deny that the highest degree of attainable accuracy is an object to be desired, and it is generally found that the last advances towards precision require a greater devotion of time, labour, and expense, than those which precede them' – Charles Babbage. Measurement in psychology and psychiatry broadly ranges from clinical impression through to psychometric assessments adorned with reassurances of interrater agreement, construct validity and test–retest reliability. In their perspective paper, Fried et al[4] explore the state of the art in measuring depression, exposing the flaws in our instruments and approaches. Some instruments (for instance, the widely used Center for Epidemiologic Studies Depression Scale) have low mean overlap with other scales, at around 31% similarity. There are 280 different published scales or instruments for studying depression, and in clinical trials

(in adolescents) 19 different primary outcome measures have been used. The correlations among scales are around 0.5 and often far lower. Fried et al conclude that we are measuring 'different depressions' and, importantly, the differences between scales used (given the heterogeneity of signs and/or symptoms captured by each) mean we should be cautious about claiming that meta-analyses – which aggregate standard mean differences or dichotomised responders – can offer high-fidelity evidence. For example, a 50% response on the Hamilton Rating Scale for Depression may not be measuring change in the same signs and/or symptoms as the same percentage difference on the Montgomery–Åsberg Depression Rating Scale. In terms of differentiating depression from controls, impressively, they show that the expected bimodal distribution of categorical 'healthy' versus 'depression' (with a clear difference in group means with roughly normal distributions) differs markedly from that reported in empirical studies of controls and patients – using over 12 000 people each administered the Depression Anxiety Distress scale and the nine-question Patient Health Questionnaire (PHQ-9), there is no clean group differentiation but rather something looking like a single roughly normal and an exponential distribution, respectively. This emphasises that 'cut-offs' (e.g. for deciding on caseness, or if one were to use PHQ-9 as an end-point for responder analyses) are somewhat arbitrary, if in a large sample of people with and without depression there is no clear bimodal distribution on the instrument.

Kaleidoscope has reported on many trials tapping into the UK's widely admired Biobank; but what if… the bank is biased? The whole principle is predicated on lots of people – about half a million – making this a highly representative sample, but perhaps someone should check that out. Well, Lyall et al[5] have done just that, exploring the psychological and physical health of those in the imaging subsample that incorporates data of about 50 000 individuals. Using *t*-tests and χ^2-tests for, respectively, continuous and categorical variables, they calculated average differences between these individuals and those who did baseline testing but did not progress to scanning ($N \sim 450\,000$) on a range of cognitive, mental and physical health phenotypes. The scanned group were consistently statistically healthier across testing, including with respect to cardiometabolic, inflammatory and neurological phenotypes. They had less depression and unhappiness, healthier lifestyles and a reduced range of physical illnesses. This also translated to the scanned having fewer cognitive risk factors.

The Biobank is a noble project despite its flaws. It has already been established that those who take part in it are more likely to be better educated, less deprived and healthier than the UK population more generally. This is an inevitable caveat to the generalisability of any of its findings. It seems from these findings that additional participation steps amplify this. The challenge for researchers will be understanding this confounder and being cognisant of it in interpreting any results.

Finally, Kaleidoscope has also reported extensively on medic burnout, but what keeps us happy and satisfied at work? It appears that the National Health Service issuing well-being cookies and 'Joy At Work' initiatives just might not be cracking it, so we need alternatives. Zhuang et al[6] report on an issue close to the Kaleidoscope team's hearts – academic affiliation. This is interesting and novel, as much on the topic of burnout has focused more on sociodemographic factors such as gender, ethnicity and family factors – clearly important but not something an individual can easily change – and work-based ones such as specialty and hours clocked in per week. Here, the authors controlled for those factors and instead took data from the US 2019 national sample survey of physicians ($N = 6000$) to test for an association between burnout and the aforementioned academic affiliation. Two-fifths of doctors had some form of affiliation, and this had a significant association with reduced emotional exhaustion and greater career-related satisfaction. It was not a completely even split: tenured professors (cough, Shergill) were doing even better than those at more lowly academic ranks (the Tracys, Albertsons and Joyces of the world). The paper notes various putative modifiers, from research opportunities through access to role models to greater opportunities for mentorship. Of course, like any career component, academia is not something everyone wants to be part of, and burnout is a complex multifactorial issue; conversely, however, we suspect that many clinicians would like greater academic involvement. It would be interesting to test with other areas of 'locus of control' and development, such as engagement in trainee teaching and other types of professional development. In an increasingly pressurised workplace, food for thought for, say, medical directors and others trying to ensure the well-being of their medics. We recommend calling yours up for a chat.

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