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Kaleidoscope

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Palcohol. What is it? It's a powdered alcohol that has recently been approved for sale in the USA. On the one hand, it is just adding choice, offering a new, crystalline form of one of the world's most commonly used and enjoyed chemicals (although recent news stories[1] of some Australians brewing moonshine from Vegemite are surely pushing choice beyond the pale). However, there are some specific challenges with palcohol, which are well articulated in an editorial in *JAMA* by Naimi & Mosher.[2] The powder is sold at 50% alcohol by weight, but the strength *by volume* will depend on how it is diluted. It can be more easily concealed than liquid alcohol, and it could be added – surreptitiously – to another alcoholic beverage. The potential for misuse, including by children, is self-evident; indeed, a video of an individual eating palcohol has already been uploaded, along with discussions on inhaling it, though such acts appear unlikely to produce intoxication. What is its current status in the UK? Answering a parliamentary question in the House of Lords earlier this year Lord Bates noted[3] that 'The Government is not aware of powdered alcohol being marketed or made available to buy in England and Wales'. However, a very quick and simple check on a well-known internet search engine gave a web-link to buy palcohol online.

Traumatic brain injuries (TBIs) can have significant neuropsychiatric sequelae, but sensitive and specific early quantifying markers of neuronal damage have been elusive. Axonal injury is one putative indicative contributor, with early lesions impacting subsequent cell degeneration. It has not been possible to adequately measure axonal injuries in living humans, but now two novel experimental methods have been tested[4] in 15 patients with severe TBIs. The first involved post-injury insertion of tiny (100 kilodalton) microdialysis catheters, measuring metabolic markers and neuronal proteins every 1–2 h over a minimum of 72 h. The second involved diffusion tensor magnetic resonance imaging (DTI) to assay white matter structural integrity at 2–9 weeks post-injury, with follow-up imaging after 1–3 years. The use of two methods allowed cross-validation of results; both (a) raised extracellular levels of the axonal cytoskeletal protein tau – but not other biomarkers – at 13–36 h post-injury and (b) anisotropy reductions in neuroimaging, proximal to the microdialysis site, were highly correlated with subsequent changes in multiple additional white matter regions. The findings, if validated against post-mortem data, will potentially allow early stratification of brain injury severity and intervention need.

At the intervention end of the process, however, TBIs have lacked effective therapeutics, though there is now some reason for optimism. Sartans are a class of drug that block angiotensin II type 1 receptors (AT1Rs), and have demonstrated neuroprotective properties. Villapol *et al*[5] tested two sartans, candesartan and telmisartan, in a mouse model of cortical impact injury. Both drugs had therapeutic windows of up to 6 hours post-injury, and reduced lesion volume, neuronal injury and apoptosis, astrogliosis, microglial activation, and pro-inflammatory signalling – as well as protecting cerebral blood flow – up to 3 days post-injury. Additionally, candesartan reduced cognitive impairment up to a month later. Drug effects were inhibited by co-administration of a peroxisome proliferator-activated receptor gamma (PPARγ) antagonist, indicating that sartans' neurorestorative properties may be through PPARγ activation as well as AT1R antagonism. PPARγ activation appears to reduce microglial and astrocyte activation, and thus cytokine and chemokine expression, while AT1R antagonism may limit post-injury vasoconstriction, reducing intracranial pressure and promoting effective blood flow. Preliminary analysis suggests that PPARγ activation may be more crucial in early stages, and AT1R blockade more important as the injury progresses.

What does it mean to enjoy good mental health? The World Health Organization's definition[6] and other recent debate pieces have moved from considering this as simply the absence of mental illness, to champion positive emotions, effective psychological functioning and social integration. The European Psychiatric Association's Committee on Ethical Issues has identified some problems with this hedonic and eudaimonic – and Western value-laden – tradition of self-mastery. They note that individuals in good mental health frequently suffer negative emotional states such as sadness and anger, that it would actually be unhealthy to feel well during such periods of duress, and that different phases of life can routinely be accompanied by perceived or real exclusion – for example, through shyness common in adolescence. Furthermore, an emphasis on social actualisation through employment may exclude many for whom this is not a viable or realistic option. The authors have put forth a novel description:

> 'Mental health is a dynamic state of internal equilibrium which enables individuals to use their abilities in harmony with universal values of society. Basic cognitive and social skills; ability to recognize, express and modulate one's own emotions, as well as empathize with others; flexibility and ability to cope with adverse life events and function in social roles; and harmonious relationship between body and mind represent important components of mental health which contribute, to varying degrees, to the state of internal equilibrium.'[7]

Adding to the complexity on what mental (ill)health means is the debate about links with creativity. One of the pioneers of game theory, John Nash, died in a car accident in May 2015; in an interview in 2002, referring to his diagnosis of schizophrenia he stated 'I wouldn't have had good scientific ideas if I had thought more normally'. Such a link has long been hypothesised (and demonstrated in epidemiological studies of patients); Power *et al*[8] have now shown how risk-prone genotypes can explain creativity going beyond the tradition of studying visible, eminent, high-profile creative individuals who have psychotic disorders. Using large aggregated analyses, a polygenic risk score for schizophrenia and bipolar disorder was derived, and then validated in a distinct sample of 86 292 individuals from the general population of Iceland. A total of 1024 individuals in the Icelandic group were identified as creative by association with national artistic societies for actors, dancers, musicians, writers and artists. Polygenic risk of bipolar disorder and schizophrenia (in the absence of actual disorder) was significantly associated with creativity with a common odds ratio of 1.17. This association was not found for five other 'non-creative' professions (farmers, fishermen, executives, manual labourers, and service/sales people) and the association with schizophrenia and bipolar risk remained after correction for educational attainment. Further, there was no association with polygenic risk and creativity status in 20 other common conditions that might involve changes in cognitive function, including attention-deficit hyperactivity disorder, Alzheimer's dementia, and dyslexia.

Studying the aetiology of psychiatric illness is compounded by the difficulties in categorical definitions of disease. This is exemplified by mood disorders, where the ICD-10 includes persistent mood disorders (F34.0 and F34.1) where disturbance

does not meet criteria for depressive episode (F32, which itself has four severity subcategories), and also a recurrent depressive disorder (F33). During the controversy surrounding the revising of DSM for its fifth edition, melancholia was argued to be a separate, more severe disorder – inadequately captured by DSM-IV as a specifier for major depression.[9] Does this offer a more coherent grouping? The CONVERGE consortium recently published results from a study of 5303 Chinese women meeting criteria for major depressive disorder (MDD) compared with 5337 controls without the diagnosis.[10] From the MDD group, a subgroup of 85% of cases ($n = 4509$) was identified as severely affected and meeting criteria for melancholia. Of 6.2 million single nucleotide polymorphisms (SNPs) extracted for this genome-wide association study, two loci on chromosome 10, at the Sirtuin1 (SIRT1) and phospholysine phosphohistidine inorganic pyrophosphate phosphatase (LHPP) regions, were significantly associated with MDD. The SNPs were then validated in a replication study from another population sample of 3231 cases of recurrent MDD and 3186 controls. Importantly, in the melancholia subgroup, the association with SIRT1 was two orders of magnitude higher than in the broader MDD group – consistent with previous findings that melancholia is a more genetically determined form of depression. The *SIRT1* gene is associated with mitochondrial biogenesis – linking the phenotype of depression to a possible molecular basis in cellular stress.

Physical changes in brain structure and cognitive impairment are well-recognised phenomena in psychotic illnesses – but what, if any, is the nature of their association? Progressive alterations in both factors have been shown to occur – at least in some individuals – but any relationship between such temporal changes had not previously been mapped. Now a case–control longitudinal study[11] has followed 84 individuals over 3 years; a relative decline in IQ was positively correlated with global cortical volume and thickness loss, with widespread changes across the frontal, temporal and parietal lobes. It remains uncertain what pathological process drives the cortical thinning, though an excess of synaptic pruning is a plausible candidate mechanism. The study finding was independent of individuals' educational level, symptom severity or duration, cannabis use and, interestingly, cumulative antipsychotic medication use.

The concern over medication-induced brain changes remains topical. A cross-sectional study[12] of 25 individuals with long-term (5–47 years) never-medicated chronic schizophrenia from China showed reductions in prefrontal and temporal cortical thickness compared with matched controls. Crucially, and uniquely, this work was able to correlate for age and illness duration, and demonstrated that the pattern was one of accelerated age-related decline in these brain regions. The patient group also showed a relative thinning in the superior parietal cortex – though this was much slowed in comparison to the other regions – and non-age-related *hypertrophic* changes in the striatum, with greater putamen volumes. The authors argue that their results confirm progressive neurodegenerative components to psychotic illness, but that different pathological processes may be at play in different brain regions.

Finally, in a world clearly preoccupied with 'selfies', a cursory perusal of Facebook confirms that our profile pictures offer a somewhat optimistically flattering portraiture. Is this positive self-projection or a form of novel narcissism? White and colleagues[13] found that individuals were more accurate in choosing high-likeness images of unfamiliar (and limited exposure) faces than of themselves, though there was low interrater reliability in general. Others, it would appear, are better at determining what we *really* look like.

Turning to a different type of self-reflection, it has traditionally been assumed that parents' attitudes towards other groups of people influence the opinions of their children, although there was an absence of longitudinal data to support this. A two-wave, 2-year study[14] evaluated how parental prejudice or tolerance towards immigrants affected their adolescent offspring ($n = 507$) over time. The results showed that influence was actually bidirectional, with adolescents also shaping their parents' views on migrants, and there was greater cohesion in the beliefs where the parent–adolescent relationship was perceived by the child to be supportive. Given widespread migration in an ever-more globalised world, the fact that adolescents might challenge and change their parents' thinking is, perhaps, a comfort; as Wordsworth taught us, the child is father of the man.

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