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Kaleidoscope

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Do long-term effects of antipsychotics contribute to the 15-year reduction in life expectancy typically found in psychosis? Iatrogenic dopamine D_2 receptor sensitisation was feared to make individuals more vulnerable to relapse, precipitating a vicious cycle wherein commencing medication could only be managed by maintaining medication. Antipsychotic use has also been associated with reduction in brain volume, and concerns raised around direct neurotoxicity and a potential contribution to cognitive symptoms and functional deterioration. However, it has been a difficult area to study, not least as there are few individuals not on some form of treatment, and methodologically, most work has been naturalistic follow-up, with obvious ethical barriers to randomised controlled trials (RCTs) denying medication to treatment-naive individuals. An impressive international expert group has reviewed the best current evidence surrounding these issues[1] and they suggest that RCTs very clearly support medication effectiveness for both acute relapse and prophylaxis; the authors note how the therapeutic effect size equates very positively with many of the most effective interventions in other branches of medicine. Correlational data support early intervention and reduced duration of untreated illness improving outcomes, and no evaluated studies reported poorer outcomes in individuals initially commenced on medication. There were few data to support concerns about long-term harm or neurotoxicity from medication: data on brain volumes were considerably confounded by underlying illness factors, and although D_2 sensitisation has been demonstrated, it has not been causally linked with worsened outcomes. The authors found that medication discontinuation and non-pharmacological interventions benefit some patients, but that such care carries risks of relapse, and we cannot currently prospectively identify for whom this approach might work best. An important read for those of us prescribing such medication, and positive information for our patients.

There is an urgent need for novel medication in treating psychosis, but the rate of discovery and clinical delivery of new agents has been glacial. We know that standard RCTs of hundreds of patients are fundamentally underpowered to determine or predict responders, and research and development costs remain prohibitive. Breen *et al*[2] describe how the Psychiatric Genomics Consortium plans a leap in genome-wide association studies (GWAS) to encompass over a million individuals in the coming few years. These, they argue, have the potential to restart stalled drug development across the study programmes of highly polygenic conditions: psychoses, major depressive disorder, bipolar affective disorder, anorexia nervosa, attention-deficit hyperactivity disorder and autism spectrum disorders. Although GWAS loci have small effect sizes, common illness-associated polymorphisms may help determine illness pathogenesis and medication targets for the development of a new range of hypothesis-led pharmacotherapies. A key step will be linking gene associations with affected biological pathways, from intracellular to brain-circuit level. Several large open-source databases are now available that can map GWAS-identified genes to transcriptomics, and identify known molecular targets of drugs. How well this will fulfil the ambition of polygenic risk scores and precision psychiatry has yet to be seen. However, it is clear that GWAS are here to stay, and potentially become part of all our lives.

Charles Darwin wrote 'Multiply, vary, let the strongest live and the weakest die'. But an individual's fitness under natural selection is complex. One reason is the phenomenon of epistasis, where the presence of one gene modifies the expression of another. The classic teaching example is hair colour: ever greater quantities of the pigment eumelanin create blonde, brown and black hair respectively; however, some individuals have a variant in another gene that interacts with this process, stopping pheomelanin conversion to eumelanin, resulting in red hair. With deleterious mutations, the fitness of an individual is, broadly speaking, inversely proportional to the mutation burden – the more mutations, the lower the fitness. Without epistasis, genes act independently and fitness decreases exponentially as a function of the number of mutations; in *synergistic* epistasis (where deleterious mutations of two alleles act together to decrease fitness more than would be expected from the independent effect of either allele) there is negative linkage disequilibrium (LD) and the variance of the mutation burden is less than the sum of each individual deleterious allele's variance. Conversely, *antagonistic* epistasis (where two mutations 'compete', yielding a smaller decrease in fitness than would be expected from the two alleles independently) results in positive LD, and the variance of mutation burden is greater than the sum of individual variances.

Using rare loss of function (LoF) alleles – which are almost always deleterious – Sohail *et al*[3] sought to establish whether they are selected under an antagonistic or synergistic epistasis assumption in humans and fruit flies. Using three whole-genome human data-sets (including Alzheimer's and amyotrophic lateral sclerosis) alongside a Zambian *Drosophila* data-set, they estimated the mutation burden, the rare LoF variance, and compared this with the variance expected without epistasis. In all data-sets, the rare LoF variance was less than that predicted by the model without epistasis – suggesting synergistic epistasis. The authors argue that humans should carry at least an estimated seven *de novo* deleterious mutations and given this, if natural selection operates on each mutation individually (i.e. with no epistasis) the result is inconsistent with the existence of the human species: this, one might consider, is a problem for most hypotheses. They suggest therefore that their results show rather that synergistic epistasis explains that humans are still undergoing negative selection, where rare deleterious alleles are removed from the population. This helps explain why high levels of variation can be maintained. There is no suggestion at any point that having red hair should be considered deleterious.

Neuroaesthetics is our word of the month, having discovered studies evaluating the impact on the brain of music and poetry. It is well-established that mood affects cognition – for example, when we are happy, we are more distractible – so Putkinen and colleagues[4] set out to test whether music might produce a similar effect. Using event-related potentials to measure auditory selective attention, participants listened to instrumental music rated as happy, neutral or sad, and thereafter undertook a listening task. For your general education, 'sad' was *Discovery of the Camp* by Michael Kamen, 'neutral' was the first movement of *La Mer* by Claude Debussy, and 'happy' was *Midsommarvaka* by Hugo Alfvén. Those listening to 'happy' sounds distributed attentional resources more widely on testing: music-induced positive mood appears to broaden the scope of auditory selection. Does that mean listening to The Smiths might help one restrict

attentional focus when studying for exams? More testing is required.

Wassiliwizky *et al* looked at the behavioural, psychophysiological, and neuroimaging changes evoked by poetry. Recited poetry – sadly, the specific poems are not detailed – was a strong stimulus for activating the brain's reward circuitry. While analogous to those changes produced by music, the authors note differences, including in the role of the nucleus accumbens, and so-called peak aesthetic pleasure can co-occur with markers of negative affect – chills and goose-bumps (piloerection measured with what was labelled the 'goose-cam'). The involvement of brain reward regions through abstract aesthetic pleasures is proposed as an explanation for the powerful human drive to seek out such experiences, including being moved by, and seeking out, tragedies. The authors cite Friedrich Schiller's definition (surely foreseeing The Smiths) of 'the mixed sentiment of suffering and the pleasure taken in this suffering'.

Continuing the poetry theme, but bringing it back to genetics, Philip Larkin's oft-cited poem, *This Be The Verse*, commences 'They f* you up, your mum and dad'.** Parental caregiving, however cynically defined, appears to have been selected into mammalian species. Bendesky *et al*[6] explore how genes contribute to parental caregiving across two mouse species, one monogamous (*Peromyscus polionotus,* PP) and the other promiscuous (*P. maniculatus*, PM). Mother and father monogamous mice (PP) both display equal caregiving behaviour to pups, but in the PM mice, fathers displayed less than mothers. Then, they placed pups from each species in foster care with parents of the other species (i.e. exposing the pups to the caregiving norms of another species) – and when these fostered mice became parents, they displayed their species-specific parental caregiving behaviour, rather than displaying (mimicking) the parental behaviour they had been exposed to as foster-pups. It appears there is a heritable and genetic component to parental caregiving. Using a genetic cross design, they mated PM females with PP males, then crossed these offspring to produce 769 mice, who were then observed for parental caregiving offered to their offspring. The resulting caregiving behaviours displayed were a mixture of their single-species ancestors in both males and females, with the exception of nest-building – suggesting that genetic loci contribute to some caregiving behaviours, but not all.

The authors then used quantitative trait locus (QTL) analyses on the genomes of the 769 mice to find 12 independent QTLs on 11 chromosomes that contribute to one or more caregiving behaviours. Of these, 8 QTLs showed effects promoting a behaviour in one sex and conversely reducing expression of the behaviour in the other sex. One QTL on chromosome 4 was correlated with nest-building behaviour when the mice were parents (but not prior to mating). In a final analysis, they identify the gene for arginine vasopressin – present in the QTL on chromosome 4 – as having the strongest association with nest-building behaviours. Direct intracerebroventricular administration of vasopressin into the PP mice inhibited nest-building behaviour, without affecting any of the other caregiving behaviours. Variation in a phylogenetically ancient neuropeptide has contributed to the evolution of parenting behaviour in mammals.

Finally, from a lot about genes to hot in jeans, and a paper we just couldn't resist sharing: clothes maketh the man, but only the man? Clearly unfazed (and, worryingly, perhaps encouraged) by our gentle teasing of his work on cats in May's Kaleidoscope, Joe Hayes shared another paper by him and UCL colleagues[7] that was, well, cat-nip to us KCL boys. A cross-sectional survey showed photographs of medics (with faces anonymised) from various specialties, training grades, and UK regions to 100 4th-year medical students. The students were asked: if they could determine the doctors' specialties and level of training; which were perceived as most professional, trustworthy, and aspirational; and – crucially – who was the most fashionable. Wearing scrubs helped identify acute care doctors, potentially adding clarity to their roles; perhaps problematically no women were identified as surgeons, with 'suits' producing such an association. Interestingly for those concerned with recruitment, medical students were most likely to aspire to follow doctors they regarded as trustworthy. However, the clear take-home valid, reliable and robust finding was that *male psychiatrists* were most fashionable and best-dressed of all medics. Our College Dean and incoming President posted a few choice comments on our Twitter feed querying this, but modesty, and our Journal language censor, forbid us from repeating them here. Science has spoken, and who are we to argue?

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3 Sohail M, Vakhruscheva OA, Sul JH, Pulit SL, Francioli LC, Genome of the Netherlands Consortium, et al. Negative selection in humans and fruit flies involves synergistic epistasis. *Science* 2017; **356**: 539–42.

4 Putkinen V, Makkonen T, Eerola T. Music-induced positive mood broadens the scope of auditory attention. *Soc Cogn Affect Neurosci* 27 Apr 2017 (https://doi.org/10.1093/scan/nsx038).

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6 Bendesky A, Kwon YM, Lassance JM, Lewarch CL, Yao S, Peterson BK, et al. The genetic basis of parental care evolution in monogamous mice. *Nature* 2017; **544**: 434–9.

7 Aref-Adib G, Sathanandan S, Hayes J, Abrol E, Duncan P, Werboloff N, et al. Guess who? How doctors' attire affects students' perceptions of their speciality. *Ment Health Family Med* 2017; **13**: 375–80.

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