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Kaleidoscope

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You're only as old as you feel – or think. Certainly, brain senescence has a disproportionate impact on individuals' abilities and degree of independence. In addition to your actual chronological age, recently developed machine learning algorithms can estimate your 'brain-age', which indexes biological health. Most work on the topic has been in Alzheimer's disease, but Elliott et al[1] used this in the large representative Dunedin longitudinal cohort of healthy individuals. They measured brain-age at chronological age 45, alongside a range of other variables including cognitive functioning and the pace of biological aging. Across the 869 middle-aged individuals, brain-age varied from 24 to 72; those with greater brain-age had accelerated ageing more generally, including an older facial appearance, supporting a 'geroscience' perspective that shared genetic, environmental and lifestyle factors were taking a toll on both body and mind. Interestingly, this was also associated with childhood lower cognitive abilities, suggesting an additional inherent vulnerability in some. Hillary et al[2] continue the theme, with the epigenetic clock darkly named 'DNAm GrimAge'. This marker of DNA methylation has previously been linked to general biological age and mortality but not cognitive functioning. The authors applied it to the Lothian Birth Cohort of 709 individuals, who had a mean age of 73. After controlling for childhood cognitive abilities, a higher DNAm GrimAge was strongly associated with lower later-life general cognitive abilities, decreased brain volume (particularly the frontal and temporal regions) and, as in other work, all-cause mortality. This association extended to a range of abnormal inflammatory markers, aligning with an 'inflammaging' hypothesis of more rapid ageing. So, two studies suggesting they can detect your biological functioning and mortality risks more accurately than the number of candles on your birthday cake.

Are there clinical applications to these perhaps somewhat macabre issues? Li et al[3] say yes, potentially in early identification of Alzheimer's disease. Although β-amyloid can appear a decade before hallmark pathology, it is currently impractical to measure it routinely. Instead, taking structural scans from the Human Connectome Project Aging cohort, the authors modelled age effects for each part of the brain and compared these data with deterioration patterns from the Alzheimer's Disease Neuroimaging Initiative. Their machine-learning proof-of-concept model produced an 'Alzheimer's disease risk' score that could identify mild cognitive impairment and had a cross-validated 94% accuracy for recognition of Alzheimer's disease. It is early days for such work: timely identification of potential problems is typically very helpful in healthcare, but of course this also opens up ethical challenges, anxieties for individuals, and the problems of false positives and false negatives. Our overall take from these three papers is that a youthful mind is a good thing, and we are already aware of many of the factors that help with that. Although none of this is currently directly pharmacologically targetable, like other aspects of health, identifying higher-risk individuals might help to nudge lifestyle behaviours that can indirectly lower risks at a more timely and effective stage. So back on your exercise bike with a wheat-grass smoothie and, more importantly, find time to laugh with friends. The Kaleidoscope team are always being told we're incredibly immature – we now realise what a compliment this is, with our brain-ages tracking to mid-adolescence.

'If you can't explain it simply, you don't understand it well enough' taught Einstein; modern analytic methods supporting clinical decision-making algorithms are complex and difficult to understand, so, who are we to disagree with him? Many of us – certainly most of the Kaleidoscope team if we're being honest – have a hard time interpreting a regression model with only a handful of variables and corresponding coefficients (or parameters). For example, how many times have you had to look up how to 'read off' an odds ratio from a logistic regression model or tried to calculate how a continuous dependent variable will change if you tweak just one of the 'inputs' or predictor variables in a linear model? Now consider that many machine learning models require *millions* if not *billions* of parameters – for example, GPT3 (which can attempt to answer questions posed to it in natural language) has 175 billion parameters. Healthcare is high-stakes; any algorithm or model that assists (or worse, replaces) a clinician making a decision should be *interpretable* or the decision delivered by the algorithm *explainable*. For example, imagine an ML system trained to decide what medication to prescribe a patient using hundreds or thousands of input variables that capture details of the patient's past medical history, comorbidity, current diagnosis and relevant investigations. You would want to know why the system recommended medication A, and which features of the patient's details it used to make this recommendation instead of alternatives B and C. Ultimately, you might want the algorithm to be demonstrably using the same information and making the same decisions *for the same reasons* as human clinicians. But how would you know if such systems are huge black boxes of millions of parameters and the system can't report the calculations (inferences) it used to deliver a decision?

Ghassemi et al[4] show that this is far from easy and, in their view, it's a false hope. They exemplify this with systems that learn to locate pneumonia in chest radiographs – some machine learning techniques; the 'hot areas' driving the machine learning system don't necessarily align with human expectations (i.e. real radiologists) even when the system is performing reasonably well. Another approach is to examine how a decision would change if the features are 'tweaked': if one increases the patient age by 10 years or changes their sex, does a different medication get recommended and is this consistent with clinical domain expertise? This is especially important in healthcare equity, when similar changes to inputs might result in *unjust* decisions, if the model cannot explain why it made a decision that violates individual healthcare rights. In psychiatric diagnosis and prognosis, we deal with inherently probabilistic abstractions of complex underlying systems or phenomena for which we have, at best, only partial mechanistic or causal explanations, requiring systems far beyond the current state-of-the-art. The authors conclude with an important observation: we have interventions (e.g. paracetamol) for which we can't offer a concrete, well-understood explanation of how they work. For this reason, we use randomised controlled trials to reassure us that in the absence of a completely physiological explanation of why an intervention *should* or *does* work, the desired health outcomes are nonetheless obtained. This lesson might well be one that artificial intelligence and machine learning researchers take to heart in persuading the healthcare community these systems are useful and safe.

The gut–brain axis has typically been studied in a cross-sectional manner in adults. But, as every nappy-changing parent will tell you, that stool microbiome in infants sure can vary: might it affect childhood behaviour? The diverse collection of bacteria, viruses and fungi that reside within our gastrointestinal tract, known as the microbiome, influences the immune system and behaviours via the gut–brain axis and has been linked to several clinical conditions including depression, anxiety, autism spectrum disorder and attention-deficit hyperactivity disorder. Studies to date have largely looked at adults already experiencing these conditions, making the directionality of the relationship between the

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microbiome and the disorders unclear. Using infants from the New Hampshire Birth Cohort Study, researchers at Dartmouth University's Geisel School of Medicine focused instead on early life,[5] before these conditions arise, when both the brain and the microbiome are undergoing rapid change. Stool samples for DNA analysis of gut microbes were obtained at 6 weeks, 1 year and 2 years of age. At 3 years old, all 260 children were given the Behavioural Assessment System for Children (BASC-2), which measures internalising, externalising and social behaviours to inform clinical diagnoses in preschool-aged children.

Bacterial diversity increased universally across the sample with age, though results overall found a time- and sex-specific influence of the microbiome on behaviour. A more diverse microbiome at 6 weeks was associated with less anxiety and depression behaviours in boys only, though levels of a particular *Granulicatella* species were a negative influence on later anxiety scores in girls. At 1 year, girls appeared to benefit from *Streptococcus peroris*, showing better depression scale scores. One might challenge depression scale scores in 1-year-olds, but these data are the first to show that host sex, even in early life before gonadal sex hormone production occurs, appears to influence the relationship between gut microbes and behavioural outcomes. Although causality is yet to be established, an opportunity to deliver potential probiotic interventions at critical windows of development gives a path to test this out and could potentially provide intervention points to support at-risk infants before symptoms emerge.

City living is a risk factor for developing many mental illnesses, but could genes have a role in determining where we live in the first place? The issue of causality has long been debated: one can think of urban 'toxins' from pollution through overcrowding to various other stressors, but the finding is not typically replicated in low- and middle-income countries. Reverse causality remains a possibility, where, for example, social selection leads more vulnerable and unwell individuals to have lower socioeconomic status that pushes them to the deprived housing and so forth more commonly found in dense urban areas. Maxwell et al[6] take a novel and far less explored approach: genetic confounding. They applied polygenic risk score (PRS) analyses to data from over 385 000 unrelated individuals in the UK Biobank. Individuals with higher PRS scores for schizophrenia, bipolar affective disorder, anorexia nervosa and autism spectrum disorders preferentially *moved* from rural to urban environments during their life. The findings do not undermine the many environmental aspects of cities that can be detrimental to our well-being, and while statistically significant, the magnitude of the association was small, but they add a twist in that our genes might also be affecting where we live. How could a gene do that, you might ask. The authors note the polygenetic nature of most mental illnesses, and the spectrum of neurocognitive traits that might influence behaviour at an illness sub-threshold level.

If urban living is a particular risk for psychoses, and as we can't change our genes, which psychosocial and psychological factors might help prevent relapse? It is less studied an area than you might suppose, with work often focusing on the more acute phase of treatment or having relapse as a secondary measure among many others. Bighelli et al[7] report a systematic review on the topic to explore the comparative efficacy and acceptability of various interventions. Eighty-five studies were included, of which 72 (covering over 10 000 participants) could be included in the first network meta-analysis of the topic. Family interventions, relapse prevention programmes, cognitive–behavioural therapy (CBT), family and patient psychoeducation, and integrated interventions (which combine different components) all reduced relapse more than treatment as usual (TAU) at 1 year. Interestingly, family interventions and psychoeducation required a year to show benefit, with no difference compared with TAU at 6 months, and we are reminded how some treatments can take time to embed. Some other intriguing time-affected data included assertive community treatment only showing efficacy at a 6 month period, and CBT not showing clear gains beyond 1 year. It's one of those papers that perhaps proves much of what you suspected or, ideally, how your service practises. But we always benefit from having the evidence to support practice.

Finally, in the movie Vertigo, after having a nervous breakdown, Jimmy Stewart is told by his friend 'I had a long talk with that woman in music therapy Johnny, and she said that Mozart's the boy for you: the broom that sweeps the cobwebs away'. She might have been onto something quite specific. There has been fascinating recent data to suggest that Mozart's sonata for two pianos in D major (K448) reduces epileptiform activity. Quon et al[8] tested this more rigorously and precisely, moving from scalp electroencephalograms (EEGs) to measuring stereo intracranial interictal epileptiform discharges (IEDs) in 16 subjects with refractory focal epilepsy. IEDs reduced by an average of just over 65% following at least 30 s exposure to this particular piece of music, with significant frontal theta activity and power in the bilateral frontal cortices. This did not occur with other musical stimuli: here, the control tasks included listening to music matched to K448 (Wagner's *Lohengrin*), music from the subject's preferred genre and a non-musical noise. So, what is happening? If solely a pleasurable, relaxing endeavour – music as therapy, as we more generally understand the concept – one might expect a range of individualised responses to lots of different types of music. Mozart as a form of non-invasive neuromodulation? It is not entirely clear, but structural decomposition of K448 to identify local and long-range nested structures in its harmonics and timbral features demonstrated that the changes to frontal theta activity occurred following shifts from longer musical segments. More work is required, but the complex patterning of the music appears to be eliciting specific neural responses. Back to our opening piece on brain aging and brain health – have a listen to K448, we think it's good for everyone's well-being: https://www.youtube.com/watch?v=3T_k45gMQUw.

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